OHSU Knight Cancer Institute

Minimal-risk Protocol

Title: EXERCISING TOGETHER© for Couples Coping with Cancer

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1.0 BACKGROUND/ RATIONALE *(REQUIRED)*

Prostate (PC), breast (BC), and colorectal (CRC) cancer survivors account for 51% of the 15.5 million cancer survivors in the U.S.[1] – a figure expected to grow by 10 million in less than a decade. Nearly all of these cancer survivors are over age 40 and are expected to live many years, if not decades, after their cancer diagnosis, raising concerns about the impact of cancer on their long-term health, work ability and health care expenses. Compared to the general population, cancer survivors have a higher risk of recurrence than their initial risk for cancer[1], dying of CVD than cancer [2, 3], and reporting functional limitations and/or an inability to work [4-8]. Cancer survivors are more likely to have multiple chronic conditions besides cancer that are associated with up to $13K in medical expenditures and $9K in lost productivity per survivor, per year [9]. Most cancer survivors are married when diagnosed and cancer will also threaten the physical and mental health of their aging spouse and the quality of their marital relationship - *in effect doubling the societal and economic impact of cancer*. Spouse caregivers experience significant health declines, such as increased CVD risk [10, 11], and are at greater risk for mobility limitations [12] and mortality than other family caregivers [13-19].

Since husbands and wives typically share environments, behaviors and values the health and wellbeing of couples becomes closely intertwined, where the physical and mental health of one partner influences the others' [20-22]. Thus, focusing solely on the survivor or spouse may miss a critical component of the cancer experience – i.e., the interdependent nature of the couple. Declining physical health of a spouse can also profoundly impact on marital quality [22-25] and chronic illness can rob a couple of intimacy, further straining the relationship. Recent evidence suggests that poor relationship quality significantly increases the risk for CVD and mortality [26-29], underscoring the need for novel ways to maintain or restore the supportive nature of the couple with cancer. Despite the threats that cancer imposes on the health of couples and recognition that the health of intimate partners is strongly intertwined, there are no evidence-based strategies in practice that <u>simultaneously address the physical, mental and relationship needs</u> of this rapidly escalating demographic of the U.S. population.

No singular program yet addresses the triple threat of declines in survivor and spouse health (physical and mental) and of their marital relationship. In the marital literature, couple-based interventions are more effective than individual-based interventions for improving individual and couple outcomes [30-32], but these approaches focus on psychosocial and relational outcomes with no attention to physical health [33]. The physical benefits of exercise for cancer survivors are recognized [34], but the potential added benefit of bringing the spouse into an exercise program with the survivor is not. Exercise may be even more important for spouses of chronically ill partners than spouses of healthy couples yet to our knowledge there are just a few controlled trials [35] targeting caregivers, and interventions were behaviorally-focused on increasing participation in aerobic activities with only one including any measure (blood pressure) related to cardiovascular health. Prior to our work, the only exercise interventions to include the spouse and patient in an exercise intervention included a non-exercising spouse as a way to improve patient adherence to rehabilitation for osteoarthritis [36] or CVD [37].

To fill this gap, we have developed an exercise strategy where the couple trains as a team to create <u>a singular approach to simultaneously improve physical, mental and relationship health of the couple</u>. *Exercising Together* is a partnered strength training program designed to improve health <u>and</u> promote teamwork by the couple. Our pilot study (1R21CA137272) of *Exercising Together* performed in a group of PC couples (n=64) was highly feasible (100% retention) and improved physical fitness, mood and affectionate behavior [38-40]. We believe these outcomes occurred because we fostered skills within the couple to better collaborate, communicate, and support one another during exercise and our conceptual model theorizes this

will lead to better physical, mental and relational health within the dyad. As a next step toward broader dissemination, we need to know if a couples-based exercise approach is similarly effective for couples coping with other cancers (and when survivor gender varies), early in the illness trajectory when a couple's relationship is most vulnerable, and at reducing risk factors for chronic illness in both partners. An equally important next step is to distinguish the unique benefits of partnered training on individual and couple health from the possible benefits of exercising in a group with others and/or of engaging both partners in a new health behavior. We propose a larger, more rigorous trial of *Exercising Together*, expanding to include couples coping early on with PC, BC or CRC, clinical markers of chronic disease risk, and comparison groups that can test the unique benefits of partnered training.

Additional background for ancillary study: Rural cancer survivors are at greater risk for a variety of poor health outcomes, even many years after their cancer diagnosis, but are the least likely to have access to programs and resources to improve their health and well-being. Improving health behaviors, such as physical activity, can have a substantial impact on quality of life and survival in cancer survivors and their partners, but rural and poor adults, and particularly cancer survivors, have low rates of physical activity. Survivors living in rural areas and/or in poverty face many barriers to exercise, particularly facility-based, supervised programs which can provide a more effective, safe and supportive engaging environment than unsupervised training. There are no studies of supervised group exercise in rural and poor cancer survivors and no studies at all, even distance-based programs, that target partners and the couple as a whole. Given our successful adaptation of *Exercising Together* to remote delivery during the COVID 19 pandemic, we may be able to extend our programs to couples coping with cancer who would never be able to participate in our parent trial.

2.0 OBJECTIVES

We propose a 3-group, 12-month (6 mos. of exercise training + 6-mo. follow-up) randomized trial in 294 couples comparing a supervised group program of *Exercising Together* to: 1) separate supervised group exercise (survivor-only and spouse/partner-only classes) and 2) separate unsupervised exercise where survivors and spouses/partners exercise on their own at home. We hypothesize that *Exercising Together* will significantly improve physical, mental **and** relationship health of couples more than separate exercise performed in a group or home setting and that benefits will persist long-term. The study addresses the following aims:

Aim 1: Determine the efficacy of *Exercising Together* on relationship quality (intimacy, communication and incongruence) in couples coping with PC, BC, or CRC.

Aim 2: Determine the efficacy of *Exercising Together* on the physical health (body composition, lipids, insulin resistance, blood pressure, inflammation, and physical function) and mental health (anxiety, depressive symptoms, fear of recurrence) of both the survivor and spouse/partner.

Aim 3: Determine how long individual and couple-level benefits from *Exercising Together* last.

Aim 4 (Exploratory): Identify the types of couples that benefit most from *Exercising Together*.

Ancillary study: We have received supplemental funding to conduct a pilot study with the following aim: Assess the feasibility and acceptability of remotely delivered supervised, group-based exercise to couples coping with cancer living in geographically underserved counties in Oregon. We will recruit an additional cohort of 30 couples (60 participants) coping with breast, prostate or colorectal cancer residing in five geographically underserved counties in Oregon (Wheeler, Malheur, Jefferson, Lake, and Benton counties). Data collected from the ancillary study will not be combined with data from the parent trial. Instead, data from the ancillary study will be compared to data collected in the parent trial to evaluate accrual, retention, and adherence rates, safety, intervention fidelity, and proportion of testing visits and measures completed. The ancillary

study will use separate recruitment materials, consent forms, and telephone screening scripts from the parent trial.

3.0 STUDY DESIGN/METHODOLOGY

The *Exercising Together* trial is a single-blind, parallel group, randomized trial comparing 3 arms: Arm 1 (experimental): *Exercising Together* where couples perform partnered exercise in a supervised, group setting versus two comparator conditions where survivors and spouses/partners perform exercise routines separately in either a supervised group setting (Arm 2) or unsupervised at home (Arm 3). All three arms will train for a 6-month period and then be followed up 6 months later. Data will be collected at baseline, 3, 6 and 12 months.

Ancillary study: Participants who enroll in the ancillary study will not be randomized. Eligible couples who agree to participate in supervised exercise will be assigned to the *Exercising Together* program. Eligible couples who decline to participate will be offered the option to enroll in the Survivor / Spouse/Partner Home Training program.

Study Arms

All Programs: Regardless of group assignment, all participants will be expected to engage in 1-hr exercise sessions, 2 d/wk for 6 months. For participants assigned to supervised exercise training, both arms will be held at the same location within a wave and in a similar block of time to aid in enrollment, but scheduled in a way to reduce contamination (i.e., there will be 15 minutes between the end of Exercising Together and the beginning of Survivor-Spouse/Partner Group classes. The latter are run at the same time, but in different rooms at a single location). Class size will be limited to 9-10 couples per class (Arm 1) or 9-10 persons in a spouse/partner or survivor class (Arm 2) so that enough attention is given to participants to ensure proper form and safety. For participants assigned to home-based training they can opt to exercise at a facility or to follow an instructional DVD at home (see below).

Functional Strength Training: The basic training program for all three study arms is a functional strength training program based on recommendations for improving muscle strength in adults [41] and our prior studies in cancer survivors. Participants wear a weighted vest while performing lower body resistance exercises (chair rises, 90° squats, lunges). By wearing weighted vests, functional exercises can be performed without encountering balance-related safety risks from handheld barbells and dumbbells. Participants use free weights (dumbbells and bands) to provide overload for upper body exercises (1-arm row, bench press, push ups, triceps extension, shoulder raise). Volume of resistance exercise, determined by intensity (weight, tailored to each individual) and duration (number of repetitions and sets), is gradually increased from low weight and high repetitions to more weight and fewer repetitions over the training period for continuous overload. Unique features of our strength training program make it particularly suitable to be performed as a partnered program even among training partners who differ in their exercise capacity. We prescribe strength training as a relative intensity so that it can be tailored for each individual. Specifically, the amount of weight placed in vests for lower body exercise is prescribed as a % of body weight, so that untrained individuals with greater body mass, reflective of absolute lean mass, begin with a higher weight than smaller individuals. For upper body exercises, the individually determined amount of weight that a participant can lift the prescribed # of times, or resistance band that a participant can complete a prescribed # of repetitions correctly, will be used to set resistance. Other paired activities, such as dance, require that both partners exercise at the same absolute intensity which likely demands different levels of effort from each individual - creating safety concerns for the partner who is expending greater effort or undertraining partners who are limited by their less fit partner. The initial training progression across the study is based on our prior work and pilot study of *Exercising Together [39, 42, 43]*. Instructors, the Project

Director and Dr. Winters-Stone will confer on a monthly basis to refine individual participant efforts across arms based on tolerance and to adjust training progression.

C.5a. *Exercising Together*: Participants randomized to *Exercising Together* will attend supervised classes led by two certified exercise instructor(s) who are trained by the study team. One instructor will focus on instructing participants on proper form and safety during training, while the second will focus on teaching and reinforcing the teamwork (i.e., communication and supportive behaviors) within the couple during exercise. Both partners will be expected to attend the same exercise sessions, but partners can attend separately in the event the other cannot, though we will discourage this except for unusual circumstances (i.e., illness). Participants attend classes along with other couples from the same recruitment wave to insure that progression of exercise is consistent among participants.

Unlike group exercise where individuals perform the same exercise in synchronized fashion led by an exercise instructor, partnered strength training requires training partners to interact with one another, verbally and physically during training. In *Exercising Together*, the survivor and his/her spouse/partner will build skills to work as a team. We will foster the skills a couple uses as they collaborate toward a common goal (e.g., improve their health and functioning). Based on our conceptual model we incorporate skills that promote and reinforce what we feel are the key characteristics of a successful team (communication, motivation, and support) and use this to guide training of couples to maximize their teamwork during each exercise session. During each exercise, one partner will assume the role of "trainer" and the other "exerciser" and then switch. We hypothesize that the teamwork skills used when training will permeate outside of the exercise setting and enhance the overall relationship of the couple. The exercise instructor focusing on teamwork will discuss the role of training partners in the early phase of the intervention and will continually work with participants to develop their roles as training partners and functioning as a team using the principles of collaboration, communication and supportive behaviors. In addition to partner roles, we will build teamwork and couple interactions by having participants perform 2-4 tandem exercises per session (i.e., lunge with ball pass, standing tandem balance). A tandem exercise is one where the couple must work together to complete the exercise. Tandem exercises require the couple to communicate and interact both non-verbally and verbally and provide a challenging but fun opportunity for direct interaction around exercise. We can modify tandem exercises if one partner is more limited than the other, yet retain the interactive element.

Survivor / Spouse/Partner Group Training: Participants will attend separate group exercise classes for survivors and for spouses/partners and a certified exercise instructor will lead each class. The way that we structure the time and location of supervised classes will allow for the two trainers leading *Exercising Together* classes to then each lead a survivor or spouse/partner group class. Survivor and spouse/partner classes will be run at the same time at the same location to make it easier for spouses/partners who need to travel together; however, they are not required to do so. Each group will follow the general functional strength training program similar to our prior studies with BC or PC survivors only [42, 43], without any element of teamwork.

Participants assigned to supervised exercise may 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.

Ancillary study: Participants enrolled in the ancillary study and assigned to *Exercising Together* will perform exercise sessions remotely as described above.

Participation in the ancillary study requires the ability to video conference with the research team. As needed, couples may be provided an Internet capable device with sufficient screen size to view the participant in a standing position (i.e., Chromebook or tablet). Devices will be collected when participation is complete.

Survivor / Spouse/Partner Home Training: Participants will be given equipment (vest, weights and/or resistance bands) and a program to do at home or a facility, depending on their preference. Within two weeks of randomization, each couple will have two one-hour training sessions with an exercise trainer who will teach them our functional strength training program, modified to their abilities and for home or facility use. We will also provide them with a general DVD of the strength program to follow at home. The trainer will check in weekly by phone in month 1 and monthly thereafter to assess tolerance and modify programs as needed. We have delivered home-based resistance training this way in our prior studies without any related injuries [42-44]. Participants can perform the program on days (allowing for 48 hours between sessions) and at times convenient for them. There is no requirement that partners exercise at the same time, though we will track the degree to which couples may do so in case we need to account for this in analyses.

Six-Month Follow-Up Period

To evaluate the persistent effects of *Exercising Together* on individual and relationship health, all couples will be followed for an additional 6 months after formal training stops. Couples may wish to maintain their exercise habits or participate in shared activities other than exercise after formal training stops and we will not discourage them from doing so. To provide couples in supervised programs a resource to continue to engage in exercise after supervised training stops we will provide them with a DVD of their programs to use at home. During the last month of supervised training we will prepare participants for the transition to unsupervised training with discussions about behavioral strategies to stay active. We will assess participation in exercise and shared activities at 9 & 12 months and consider these behaviors in analysis for Aim 3 (see **Analysis Plan**). We will also repeat all measures at month 12 in order to better assess the residual effects of *Exercising Together* among couples that do or do not continue to exercise or engage in shared activities in the follow-up period.

Participant safety. None of our participants have dropped out of a study due to an injury related to exercise training; however, as with any study in older adults, exercise adherence has been affected by minor musculoskeletal complaints that usually stem from pre-existing orthopedic conditions. We will reduce the risk of injury and symptoms that might limit exercise adherence by: 1) required physician clearance for every participant and 2) monitoring and early care of musculoskeletal symptoms**.** If a survivor develops metastatic disease during the study his/her data from the point of the diagnosis will be considered separately, but s/he could continue in the study program with physician clearance.

Participant Incentives: Remuneration will be provided to couples based on completion of each study related activity as outlined in the table below, at each of the four main time points (baseline, 3-months, 6-months, and 12-months).

To offset travel burden for couples who live outside of the Portland metro area, a $25 remuneration will be provided at testing visits for couples whose travel exceeds a 60-mile roundtrip. In addition, we will provide 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. The total travel compensation will not exceed $100 per testing time point for a maximum total compensation of $400 per couple. When travel exceeds 150 miles roundtrip, the couple may be provided with one night of hotel accommodations in the OHSU vicinity.

A couple completing only remote testing and surveys will be compensated $35 per visit, for a total of $140 over the course of their one year enrollment.

A couple traveling less than 30 miles from OHSU and completing in-person testing, blood draw, and surveys will be compensated $85 ($100 with remote testing) per visit, for a total of $340-$400 over the course of their one year enrollment.

A couple traveling ≥ 60 miles roundtrip from OHSU and completing in-person testing, blood draw, and surveys will be compensated between $110 and $185 depending on mileage ($125-$200 with remote testing), for a total of $440-$800 over the course of their one year enrollment.

Study Activity	**Compensation per time point*, per couple**
Surveys	$20
Performance testing – remote	$15
Performance testing – in-person	$25
Blood draw	$40
Travel ≥60mi roundtrip from OHSU	$25 + $0.17/mi outside of 30mi, max $100 total
Travel ≥150mi roundtrip from OHSU	1 hotel night

*Time points: baseline, 3-month, 6-month, and 12-month

Ancillary study: Participants enrolled in the ancillary study will participate remotely and will not be asked to travel, therefore they will not receive remuneration for travel.

Participants in the ancillary study may be provided with a small monthly remuneration (up to $10 month for 7 months) to help offset costs of broadband and/or cellular services needed to participate.

Measures and Data Collection

Outcomes data will be collected at 0 (baseline, just prior to randomization), 3 (mid-intervention), 6 (post-intervention), and 12 months (6 mos. after completion of the intervention (follow-up)). Written surveys are completed on a computer at the testing facility at baseline and online for follow-up visits. All measures are completed by both members of the couple at each wave.

Primary Outcome Measure:

1. Dyadic coping
   Measured by the Relationship Focused Coping Scale to assess the degree with which couples practice active engagement and protective buffering using questions on a scale from 1 (never) to 5 (very often).

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

2. Emotional intimacy
   Measured by the Dyadic Adjustment Scale (DAS) to assess each partner's satisfaction with their relationship by answering questions on a 6-point scale ranging from 1(always agree) to 6 (always disagree).

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

3. Physical intimacy

Measured by the Physical Intimacy Behavior scale which asks participants the frequency that they engage in, initiate, and avoid intimate behaviors using questions on scale from 1 (none of the time) to 4 (most or all of the time).

[Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

4. Concealment of symptoms
   Measured by the Emotional-Intimacy Disruptive Behavior Scale. Patients report the extent to which they engage in 8 behaviors using a scale from 1 (rarely or none of the time) to 4 (most or all of the time).

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

5. Symptom incongruence
   Measured by the degree of agreement between the survivor and spouse/partner ratings of the survivor's pain, fatigue and physical function in the past week using the following instruments: the Brief Pain Inventory (BPI) to measure pain intensity and pain interference, Functional Assessment in Chronic Illness Therapy (FACIT) fatigue survey to measure fatigue, and perceived physical function using a subscale of the SF-36 medical outcomes survey (all described below).

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

Secondary Outcome Measure:

6. Body composition
   Measured by bone-free lean and fat mass (kg) for the whole body determined from a whole body dual energy x-ray absorptiometry (DXA) (Hologic-QDR Discovery Wi; APEX software, v.4.02) scan and used to calculate the % body fat.

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

7. Cardiovascular health: serum fasting lipids
   Measured by serum fasting lipids (total, high-density and low-density lipoprotein cholesterol and triglycerides)

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

8. Cardiovascular health: insulin resistance
   Measured by Homeostasis Model Assessment – Insulin Resistance - HOMA-IR: as the product of glucose and insulin, obtained from a fasting blood sample, divided by a constant.

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

9. Cardiovascular health: resting blood pressure
   Measured by the average of three consecutive resting blood pressure measurements (systolic and diastolic pressures).

   [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

10. Inflammation
    Measured by serum levels of high sensitivity C-reactive protein (hsCRP) and tumor necrosis factor alpha (TNF alpha) obtained from a fasting blood sample.

[Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

11. Objective physical function
    Measured by the Physical Performance Battery (PPB) to determine a person's ability to perform daily tasks independently. The PPB consists of 3 timed tests: 5 repeated chair stands, standing balance, and gait speed over 4 meters. Each test is scored 0 (unable) to 4 (completes without difficulty), based on quartiles of performance, then scores are summed. The possible range of scores is 0-12.

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

12. Quality of life (QOL): QLQ-C30 and SF36
    Measures QOL in cancer patients including subscales of physical and mental functioning. The SF-36 Health Survey assesses QOL in the general population.

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

13. Depressive symptoms
    Measured by the Center for Epidemiological Studies-Depression (CES-D) scale to determine the degree of depressive symptoms.

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

14. Anxiety
    Measured by the PROMIS anxiety short form using questions on a scale ranging from 1 (never) to 5 (always).

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

15. Fear of recurrence
    Measured by the Fear of Recurrence scale to assess the amount of concern survivors have about their cancer returning in the future. Participants respond to questions ranging from 1 (strongly agree) to 5 (strongly disagree).

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

Other Pre-specified Outcome Measures:

16. Sexual function
    Measured by the NIH PROMIS® Sexual Function and Satisfaction survey

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

17. Caregiver strain
    Measured by the 18-item Multidimensional Caregiver Strain Index and the 6-item Role Overload scale.

    [Time Frame: 0 baseline (just prior to randomization), 3, 6, and 12 months]

Descriptive Measures

Demographic variables, including age, education, income, insurance status, length of relationship, cancer type and treatments (survivor), medications and health habits will be measured at baseline by an in-house questionnaire and updated at subsequent visits. Clinical measures of weight and height will be made.

Presence of chronic medical conditions, used to characterize the health of the sample, will be measured by the Charlson Comorbidity Index,[85] a weighted index originally developed to predict mortality.

Shared activities at each time point will be measured using 2 items developed and used by this team. Survivors and spouses/partners are asked to rate engagement in a) leisure activities together and b) exercise activities together on a 0-4 scale, with a follow-up open-ended question about types of activities engaged in.

Process Measures

Adherence. Adherence (% of prescribed sessions completed) will be tracked from attendance logs recorded by the exercise instructor to describe dose of exercise so that we can interpret and generalize our findings. Additionally, a single-item likert question will be asked of survivors and spouses/partners regarding how supportive they felt their partner was to them during the program and how supportive they felt they were to their partner.

Establishing the training effect and dose of exercise. Documenting the presence and degree of a training effect from experimental programs is an important element of any exercise training study[86]. In the absence of these measures it would be difficult to interpret unexpected, i.e., null, study findings. The improvements in fitness from exercise training are also an indicator of the dose of training, which can be used to interpret study outcomes. Evidence that the *Exercising Together* program effectively increased muscle strength will be evaluated by 1-repetition maximum testing for leg press and bench press. We have used the 1-RM technique in 6 studies of cancer survivors (age range: 35-89 y.o.) with no adverse events. The 1-RM test will be conducted according to established protocols[87]. Our in-house CV for this measure is 0.05-0.06[88]. During periods of hospital recommendations for decreased in-person contact, the 1-repetition maximum testing for leg press and bench press will be substituted with a push-up test and plank test. These measures can be completed through video conferencing. To establish testing validity, these measures may also be completed in the testing lab when in-person contact resumes.

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Additional Outcomes

Physical activity (PA): To determine whether or not participation in *Exercising Together* changes overall PA levels and to compare our data against other studies that measure PA by self-report we will administer the 41-item Community Healthy Activities Model Program for Seniors (CHAMPS) PA questionnaire[88]. CHAMPS is a widely used and reliable[89] measure of PA in older adults that we've used in cancer survivors[38, 90-92].

Postural and dynamic stability will also be tested using the Mobility Lab ISWAY test and 6-min walk (APDM, Inc., http://apdm.com). The instrumented versions of the 6 min walk test and the Static Balance Test incorporate the use of wearable sensors to electronically detect changes in mobility beyond simple time measures or subjective scales. For each test, participants will wear six watch-sized movement sensors strapped to the wrists, ankles, chest, and waist using Velcro bands. The ISWAY consists of a 30-second trial of standing quietly and captures the amplitude, frequency, velocity and jerkiness of postural sway in multiple directions. This test will be completed once with the eyes open, feet together and once with the eyes closed, feet together. Postural sway is associated with balance control, is a strong predictor of falls, and is worse in those with neurological impairment.[Mancini & Horak, 2010]

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 a modified version of the Cancer Loneliness Scale to spouses/partners in which language referring to the cancer survivor is revised to refer to the cancer survivor's intimate partner. We will administer the CLS and the modified CLS to newly enrolled participants.

Intervention Feedback: To better assess program feasibility and acceptability, as well as capture participant experiences not possible from our standardized surveys, we will be administering a survey (Post-Intervention Survey) at the end of the 6-month intervention that includes both qualitative and quantitative questions about the participant's experience in their assigned exercise program.

Study visits may be delivered in-person with additional precautions during periods of hospital recommendations for decreased in-person contact, 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 (self-report collected if in-person assessment not expected)
2. Weight
3. Physical Performance Battery (PPB) (see 11. Objective physical function above, under Secondary Outcome Measures)
4. All surveys (see 1-5 above, under Primary Outcome Measures, and 12-17 under Secondary Outcome Measures and Other Pre-specified Outcome Measures) 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.

To assess upper body strength remotely, novel assessments to this trial will include:

5. Push-up test
   Measured by the number of push-ups completed in one continuous bout until fatigue
6. Plank test
   Measured by the amount of time in seconds that the participant is able to hold a plank position

The following measures will not be collected remotely:

1. DXA scan (see 6. Body composition above, under Secondary Outcome Measures)
2. Resting blood pressure and blood draw (see 7-10. Cardiovascular health/Inflammation above, under Secondary Outcome Measures)
3. Postural and dynamic stability (see Additional Outcomes above)
4. 1-repetition maximum testing for leg press and bench press (see process outcomes above)

Ancillary study: All study visits will be conducted remotely via videoconferencing. Measures will be collected in accordance with remote testing procedures described above.

4.0 STUDY POPULATION

For this study, we will recruit prostate, breast and colorectal cancer survivors and their co-residing spouse/partner, including both heterosexual intimate partners and same-sex couples.

We aim to recruit 294 couples (588 participants).

Ancillary study: We will recruit an additional 30 couples (60 participants) from five geographically underserved counties in Oregon (Wheeler, Malheur, Jefferson, Lake, and Benton counties).

5.0 INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria: *Survivors Only*:

- Histologically confirmed PC, BC or CRC without evidence of metastatic disease (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 or her physician)
- Three years or less from diagnosis date, by month and year, at time of enrollment *(*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 or her physician)
- Completed treatment (e.g., surgery, radiation and/or chemotherapy) ≥6 weeks prior to enrollment. Concurrent adjuvant hormone therapy is permitted and must have been initiated ≥ 6 weeks prior to enrollment. For prostate cancer, Androgen Deprivation Therapy (ADT) may constitute primary treatment and must have been initiated ≥ 6 weeks prior to enrollment. For breast cancer, hormone therapy may constitute primary treatment and must have been initiated ≥ 6 weeks prior to enrollment. (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 or her physician)
- Co-residing with an intimate partner or spouse who is willing to participate (confirmed by self-report on Health History Questionnaire)

Inclusion Criteria: *Survivors and Spouses/Partners*:

- Age 35-80 years (confirmed by self-report on Health History Questionnaire)
- Underactive (< 2 strength training sessions per week, lasting 30 minutes or more per session, at a moderate intensity in the last month) (confirmed by self-report on Health History Questionnaire or by discretion of the Principal Investigator)

Exclusion Criteria: *Survivors and Spouses/Partners*:

- Cognitive difficulties that preclude answering the survey questions, participating in the exercise classes or performance tests, or providing informed consent as determined 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. Specific contraindications include the following: declared pregnancy, poorly controlled diabetes, recent cardiac event, neuromuscular disease, untreated orthostatic hypertension, recent surgery, acute hernia, acute rheumatoid arthritis, severe memory disorders, severe balance disorder, inability to ambulate (use of an assistive device permitted), inability to stand for 3 minutes,

severe hearing or vision problem. (For Survivor: Confirmed by physician clearance; For Spouse/Partner: must answer 'No' to American College of Sports Medicine pre-participation screening questions [103]. If spouse/partner answers 'Yes' to either question they will be considered eligible upon physician clearance. Physician clearance may also be requested at the discretion of the Principal Investigator. For either: absence of pregnancy in persons who could possibly be pregnant but have not declared a pregnancy at screening, will be further screened with a pregnancy test administered at each testing visit, unless only participating remotely.)

- 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_Exercising Together")

- 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_Exercising Together" or the professional opinion of the Principal Investigator, Dr. Kerri Winters-Stone.)

Ancillary study: Participants recruited for the ancillary study will not be screened with a pregnancy test due to remote participation.

Ancillary study: To expand the pool of eligible participants, we will including survivors with a longer interval since diagnosis, as below.

Survivor only inclusion criterion:

- Ten years or less from diagnosis date, by month and year, at time of enrollment *(*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 or her physician)

Ancillary study: Additional exclusion criteria:

- Insufficient internet connectivity to support videoconferencing (Confirmed by documentation in the Case Report Form titled "CRF - Participant Contact Info_Exercising Together")

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, breast or colorectal cancer.

7.0 SETTING (REQUIRED)

The primary study site will be Oregon Health & Science University (OHSU). Testing will be conducted at the OHSU Knight Cancer Research Building and the Oregon Clinical Translational Research Institute (OCTRI). Exercise training will be offered at OHSU and several community sites serving different geographic regions of the Williamette Valley, including an exercise site in Salem, OR, 60 miles south of Portland so that we can develop and test features of delivering the program outside of a large urban area. Study visits and exercise training may be delivered remotely via video conferencing. 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.

Ancillary study: For participants enrolled in the ancillary study, study visits and exercise training will be delivered remotely via video conferencing.

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_20191210*. 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_20191210*. 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 - Phone Screen_Survivor_revised 20190212*.

Interested participants will be screened either by phone or in person using an IRB approved screening script. After initial screening, interested and eligible couples will come to the OHSU Knight Cancer Research Building and will be presented with an online IRB-approved Consent Form prior to any study-related procedure. The Consent Form will describe the goals of the study, study procedures, confidentiality, risks, benefits, and voluntary nature of the research. After participants view the consent online, and click the box that they have read and agree to participate (indicating that they have signed the consent), they will be sent links and requested to complete REDCap surveys. For the baseline testing session, couples will be asked to provide a fasting blood draw (which may be completed at an appointment separate of the baseline consenting visit but prior to initiation of the intervention), blood pressure, DXA scan, physical tests (PPB, 1RM leg and bench press, standing balance, and 6 minute walk test), and questionnaires. The testing session will take ~2-3 hours per couple, initially, and will be repeated at 3, 6, & 12 months and only take 1-2 hours. Following baseline testing, the Project Director will provide each couple with an envelope that contains their random assignment to a study group in order to retain blinding of the research assistants who conduct testing. Couples will be randomly assigned to 1 of 3 groups: 1) *Exercising Together, 2) Separate survivor / spouse/partner group exercise* 3) *Separate survivor / spouse/partner home exercise*. Enrollment will be stratified by cancer type and average couple age (<60 vs. 60-80). Assignment will be in random blocks of 6-9 couples for even enrollment.

During periods of hospital recommendations for decreased in-person contact, re-consent for the 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 couples 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.

Ancillary study: Individuals being recruited for the ancillary study will be screened by phone or videoconference using an IRB approved screening script, including screening questions about their internet connectivity and computer hardware for remote study participation. In order to assess participants' ability to participate in videoconferencing, they may be asked to facilitate gathering information about their internet speed from their internet service provider. After initial screening, interested and eligible couples 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. If a participating couple is provided with an internet-capable device (i.e. Chromebook or tablet), they will sign a Device Agreement prior to receiving the device.

Intervention, tests or procedures:

Regardless of group assignment, all participants will be expected to engage in 1-hr exercise sessions, 2 d/wk for 6 months. The basic training program for all three study arms is a functional strength training program based on recommendations for improving muscle strength in adults[41] and our prior studies in cancer survivors. 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 couples will be followed for an additional 6 months after formal training stops. Couples may wish to maintain their exercise habits or participate in shared activities other than exercise after formal training stops and we will not discourage them from doing so. To provide couples in supervised programs a resource to continue to engage in exercise after supervised training stops we will provide them with a DVD of their programs to use at home.

All biomarkers of inflammation and cardiovascular health will be measured from blood obtained from participants by the Oregon Clinical Translational Research Institute (OCTRI), following established protocols. Participants will be asked to fast and abstain from smoking cigarettes, drinking alcohol or drinking caffeinated beverages for 12 hours before the blood is drawn.

The total duration of an individual subject's participation in the study is 12 months. Certain data (questionnaires and adverse events follow-up) may be collected after this 12-month period, when a participant is off study, using IRB-approved language. With participant approval, we may contact a patient's provider to confirm cancer history.

When participants drop out of the research their data will be retained for analysis. If a participant becomes ineligible during the study s/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.

Drop out of one exercise partner in Exercising Together arm: If one partner of a couple is unable or unwilling to continue exercise training, any data collected on them prior to their withdrawal will be used for purposes of this research. Data will be continued to be collected on the other partner and they will be allowed to continue in the exercise program. If needed their program will be adapted so that it can be performed independently.

The investigator may choose to withdraw a participant without their consent if his/her health changes and the study is no longer in their best interest, if new information becomes available, if he/she 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	3-Month Testing	6-Month Testing	9-Month check-in	12-Month Testing	Monthly - Month 1 – 12
Pre-screening eligibility	X							
Consent form	X							
Exercise (intervention)			X					
Dyadic Coping		X		X	X		X	
Emotional intimacy - DAS		X						
Concealment of symptoms – EIDB Scale		X		X	X		X	
Physical intimacy – The Physical Intimacy Behavior Scale		X		X	X		X	
Pain - BPI		X		X	X		X	
Fatigue - FACIT		X		X	X		X	
Depressive symptoms – CES-D		X		X	X		X	
PROMIS Anxiety		X		X	X		X	
Fear of recurrence – F.O.R. scale		X		X	X		X	
Demographics – demographic questionnaire		X						
Comorbidities – Charlson Comorbidity Index		X		X	X		X	
Shared activities		X		X	X		X	
Physical activity - CHAMPS		X		X	X		X	
Quality of Life – QLQ-C30 & SF-36		X		X	X		X	
Sexual Satisfaction – PROMIS Sexual Satisfaction Survey		X		X	X		X	
Care strain – Role Overload; Multidimensional caregiver strain index (MCSI)		X		X	X		X	
Cancer-related Loneliness – Cancer Loneliness Scale		X		X	X		X	
Post-Intervention Survey					X			
Inflammation & cardiovascular health--blood draw		X		X	X		X	
Exercise Follow-up Survey						X	X	
Adverse Event Survey								X
Body composition-DXA		X		X	X		X	
Resting Blood Pressure		X		X	X		X	

Procedures	Eligibility Screening	Baseline Testing	Intervention	3-Month Testing	6-Month Testing	9-Month check-in	12-Month Testing	Monthly - Month 1 – 12
Physical functioning-PPB, iSWAY, 6-minute walk		X		X	X		X	
Muscle strength-1RM leg & bench press		X		X	X		X	
Push-up test*		X		X	X		X	
Plank test*		X		X	X		X	

*Conducted during remote testing visits. For validity purposes, these measures may also be completed in the testing lab when in-person contact resumes.

Ancillary study: **SCHEDULE OF EVENTS**

Procedures	Eligibility Screening	Baseline Testing	Intervention	3-Month Testing	6-Month Testing	9-Month check-in	12-Month Testing	Monthly - Month 1 – 12
Pre-screening eligibility	X							
Consent form	X							
Exercise (intervention)			X					
Dyadic Coping		X		X	X		X	
Emotional intimacy - DAS		X						
Concealment of symptoms – EIDB Scale		X		X	X		X	
Physical intimacy – The Physical Intimacy Behavior Scale		X		X	X		X	
Pain - BPI		X		X	X		X	
Fatigue - FACIT		X		X	X		X	
Depressive symptoms – CES-D		X		X	X		X	
PROMIS Anxiety		X		X	X		X	
Fear of recurrence – F.O.R. scale		X		X	X		X	
Demographics – demographic questionnaire		X						
Comorbidities – Charlson Comorbidity Index		X		X	X		X	
Shared activities		X		X	X		X	
Physical activity - CHAMPS		X		X	X		X	
Quality of Life – QLQ-C30 & SF-36		X		X	X		X	
Sexual Satisfaction – PROMIS Sexual Satisfaction Survey		X		X	X		X	
Care strain – Role Overload; Multidimensional caregiver strain index (MCSI)		X		X	X		X	
Cancer-related Loneliness – Cancer Loneliness Scale		X		X	X		X	
Post-Intervention Survey					X			
Exercise Follow-up Survey						X	X	
Adverse Event Survey								X
Physical functioning-PPB		X		X	X		X	
Push-up test		X		X	X		X	
Plank test		X		X	X		X	

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 Knight Cancer Research Building. Documentation of the consent process and a copy of the signed consent will be maintained in the patient's medical record.

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 used and collected for purposes of this study will be stored until data analysis is complete and then the data will be transferred to a repository. All data received from OSCaR for purposes of eligibility/recruitment purposes will be destroyed after the purposes of the research have been fulfilled. Electronic files will be deleted from the secured drive used by the study team.

b) Sharing of Results with Subjects

Results of the physical tests will be shared with the subjects

c) Data and Specimen Banking

Specimens and data from this study will be banked in a repository for future use as part of this protocol. Data may be stored indefinitely while blood samples will be stored for no more than 20 years. Access to data/specimens is restricted to study personnel. Data/specimens released to other investigators will be labeled with only the code assigned to each participant at enrollment. This same unique identifier, along with the date of specimen collection, will be used to label blood samples taken and for storage.

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 phlebotomy and radiation exposure. With respect to venipuncture procedures in general, some participants may experience temporary discomfort. Extremely rare risks associated with venipuncture are bleeding, fainting or feeling lightheaded, hematoma, or infection. With respect to 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.

Ancillary study: Participants in the ancillary study will not incur risks from phlebotomy or radiation exposure. Participants in the ancillary study may be provided with an internet-capable device (i.e. Chromebook or tablet) to help them access the study, and use of the device may pose a risk of loss of confidentiality/privacy.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

The Oregon State Cancer Registry (OSCaR) will be the primary means 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.

Potential participants will be identified by OSCaR for their cancer type (prostate, breast, colorectal), cancer treatment (surgery, radiation and/or chemotherapy), age, 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.

Potential participants will also be recruited via a study information mailing through the OHSU Cancer Registry and interested participants will contact us if they would like to learn more about the study and to check for eligibility. In addition we will recruit at community events, such as patient conferences and fundraisers, through study advertisements placed through various media outlets (i.e., internet, newspaper, radio), and by referral from the OHSU Prostate Cancer Clinic.

Ancillary study: Participants may also be recruited through the Oregon Office of Rural Health or the Oregon Rural Practice-based Research Network.

Members of tthe research team, 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. Participants will also visit the OHSU Oregon Clinical Translational Institute for a blood draw collection at each measurement point.

Ancillary study: Participants in the ancillary study will participate remotely and will not visit OHSU.

b. Protection Against Risk

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 any of the study exercise programs prior to beginning exercise training. If a wo/man's physician does not clear him for participation we will inform the participant and refer him/her 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 document and 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, s/he will be told s/he can stop answering research questions, or participating in performance or clinical testing, and begin again at a later time. 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 Winters-Stone, 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.

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.

To minimize risks associated with phlebotomy, all venipuncture will be conducted by trained personnel from the Oregon Clinical Translational Research Institute (OCTRI) nursing services staff in adherence with OHSU Patient Care Services policy on venipuncture techniques for blood sampling. Serum samples will be labeled with participants unique study identifiers and will be subsequently stored in the OCTRI core laboratory. OCTRI is supported by the NIH specifically for the purposes of translational research, and the OCTRI core laboratory performs all procedures in accordance with guidelines issued by the Clinical and Laboratory Standards Institute, American Association for Clinical Chemistry, American Society for Clinical Pathology and other professional organizations appropriate to each specialty. To minimize risk against excess radiation exposure from DXA, whole body DXA scans will be conducted by the RA who will have been trained by the Principal Investigator and/or Project Director. Whole body DXA scans will be performed according to standard protocols which allows for early repositioning to minimize patient exposure.

Ancillary study: Participants in the ancillary study will not incur risks from phlebotomy or radiation exposure.

Participants in the ancillary study may be provided with an internet-capable device (i.e. Chromebook or tablet) to videoconference with the research team. To minimize risks to participant confidentiality/privacy, participants will be asked to only use the device for study-related activities, and we will recommend that participants lock the device with a password when not in use.

11.0 POTENTIAL BENEFITS TO SUBJECTS

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

12.0 TIMELINE & MILESTONES

Project Timetable	Y1				Y2				Y3				Y4				Y5			
	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						
Recruit, enroll, baseline visit			W1	W2	W3	W4		W5	W6	W7	WG	W8	W9		W10					
Start 6-month intervention			W1	W2	W3	W4		W5	W6	W7	WG	W8	W9		W10					
Mid- & post-intervention visits				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
6-month follow up visit					X	X	X	X	X	X	X	X	X	X	X	X	X	x		
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 10 waves (W1, W2, …); WG = geographically underserved wave (ancillary study); Quarters are approximate time points

13.0 BIO-STATISTICAL CONSIDERATIONS

Power and Sample Size

Required sample size was derived for the outcomes of Aim 1. Power analysis using traditional assumptions of the repeated measures ANOVA model suggest that as few as 174 couples would be necessary to detect a small effect (d=.20) between groups over time, an effect smaller than the observed effect on affectionate behavior in spouses/partners in our previous work[40]. However, these traditional power calculations are known to be optimistic. While there are good power formulae for MLM clustered designs and repeated measures designs, as yet there is no specific formula for calculating power for dyadic analyses. Using a formula provided by Raudenbush and Bryk[104, 105] for individual repeated measures and estimates from our previous dyadic models, we calculate a sample of 264 couples measured 4 times over a 12-month period has a power of 0.80 to detect a moderate effect (d=.40) on change over time. As dyad models using MLM control for interdependence between members of the couple, power is increased over an individual model. We, therefore, believe this to be a more conservative estimate of power. Further attempts to increase power and reduce Type I error will be to use the omnibus hypothesis-testing procedure in the HLM program. Another rule-of-thumb is to require a minimum number of subjects per parameter estimated. Even in the most complicated model, the proposed sample of 264 couples would exceed the minimum standard of 5-10 subjects per parameter estimated.[106] No universal approach has been adopted for sample size considerations in GMM and this will be used in an exploratory aim; however, our n-to-items ratio exceeds sample size recommendations for related approaches (10-20:1).[107] In sum, the proposed sample size of 264 couples is on par with our previous trials and will allow us to detect clinically meaningful change and address study aims. To insulate the sample size against an estimated attrition of 10% across the study period, 294 couples will be randomized. The attrition estimate is more conservative than our prior trial of *Exercising Together* where no couples in the exercise program dropped out and the drop out in our current GET FIT trial that average 6% for a 6-month intervention. Couples will be enrolled into 10 waves (a new wave begins every 3-4 months) of 9-10 couples to maintain reasonable class sizes and make efficient use of testing resources. We will recruit approximately even numbers of couples coping with each type of cancer (N=98 per disease site) and stratify by cancer type at randomization.

Analysis Plan

Standard descriptive statistics/graphics will be used to check for any departures from statistical assumptions (e.g., normality, outliers, etc.).[108] We will examine dropout and patterns of missing data to determine mechanisms (MCAR, MAR, or not ignorable). In the case of data missing MCAR or MAR, model-based maximum likelihood estimation available in the MLM approach will allow unbiased parameter estimation using all available data (i.e., missing data is handled efficiently

with no loss of information).[109, 110] If the rate of attrition is high and missing data is not ignorable, we will continue with the planned analyses but temper our conclusions. For each aim, we will conduct intention-to-treat (ITT) and completers only analyses. ITT analyses will include all participants regardless of adherence to exercise regimen. Based on median attendance data from our prior trials, completers will be defined as participating in 50% or more of the scheduled exercise sessions. We will track medical treatment changes, cancer recurrence, and adherence to exercise. Age, comorbidities and time since diagnosis will be considered as covariates in all analyses. All analyses will be conducted in R and HLM statistical software packages (Aim 4 will be conducted using MPlus v7.2).

Aim 1: Determine the efficacy of partnered strength training on relationship quality (intimacy, communication and incongruence)**.** A longitudinal multivariate-outcomes dyad model will be used to directly examine couple trajectories in intimacy (emotional & physical) and communication over time. This is a multi-level model where responses from the survivor and spouse/partner are modeled simultaneously to control for the interdependent nature of the data and autocorrelation among repeated assessments. These models have been described and used extensively by Co-PI Lyons.[22, 111-113] The Level 1 model has four coefficients representing intercepts (baseline assessments) and slopes (rates of change) for survivors and spouses/partners that become outcome variables in a Level 2 model. Models with linear and quadratic change across time will be compared to determine best fit to the data. Aim 1 will be addressed with Level-2 models that include dummy variables to directly examine the effects of the partnered intervention vs. supervised individual (dummy 1) and unsupervised individual (dummy 2) exercise groups on individual level changes (controlling for couple effects) in intimacy and communication across time. A significant group coefficient on the slopes at level 2 and significantly better fitting model (evidenced by deviance statistic) will indicate the rate of change across time is different depending on a treatment group (i.e., interaction effect). We will also explore the efficacy of *Exercising Together* on incongruence (regarding survivor pain & fatigue) in couples. Univariate-outcomes models will be used to generate Empirical Bayes estimates of the gap between survivor and spouse/partner over time for each symptom measure. This comprehensive approach to estimating incongruence has been described elsewhere[114-116] and successfully used by this team.[55, 63, 113, 117, 118] The effect of *Exercising Together* on incongruence will be directly tested (similar to above model) by a significant coefficient for one of the two GROUP variables on the slope parameter and significantly better fitting model.

Aims 2: Determine the efficacy of partnered strength training on physical and mental health. Separate longitudinal multivariate-outcomes models will be used to directly examine the effect of partnered strength training in couples on each physical (body composition, lipids, insulin resistance, blood pressure, inflammation, and physical function) and mental health outcome (anxiety, depressive symptoms, fear of recurrence) as described above under Aim 1.

Aim 3: Determine the persistence of Exercising Together**.** Sustained effects will be tested by comparing linear and quadratic trajectories across time (as discussed above). We will also separately estimate and directly compare the intervention effects between the intervention (baseline to 6 months) and follow-up (6 months to 6 months after end of intervention) periods.

Aim 4: Exploratory analyses: Patterns and predictors of types of couples who benefit the most. GMM identifies distinct patterns of change that vary around different means, have unique variance and homogenous within-trajectory growth. Based on conditional probabilities, cases are assigned to the “most likely class” or pattern of change over time (e.g., couples who benefit/improve most from the intervention). Couple-level estimates from Aims above will be integrated into progressive GMM to determine if there are distinct and naturally-occurring patterns of change in outcomes over time with the dyad as the unit of analysis. Survivor-, spouse/partner- and couple-level

determinants of fitting one pattern of change over the other(s) will be modeled using logistic, multinomial or ordinal regression as appropriate. This integrated multilevel and mixture modeling approach has been used previously by this team,[118] as it allows us to identify types of dyads and differentiate them based on individual and couple-level factors. Finally, based on our pilot, we expect the intervention to have a positive effect on relational outcomes although it is possible that in a larger trial a small subgroup of couples will experience poorer outcomes; identifying characteristics of each common type of couple will allow interpretation of the generalizability of our findings.

Additional Analyses: Gender as a Moderating Variable: We will also explore the moderating effect of gender on the effectiveness of *Exercising Together* in couples coping with different cancers (e.g., do women benefit more than men) after controlling for role (i.e., survivor vs spouse/partner). Interaction terms will be added to models described above to test for moderating effects.

Ancillary study: Feasibility and acceptability of the ancillary study will be determined by calculating accrual, retention, and adherence rates, number of adverse events, and the proportion of testing visits and surveys completed. Feasibility and acceptability metrics will be compared to those of the parent trial.

14.0 RECRUITMENT METHODS

We have planned for a 36-month enrollment period (see *Timeline*) to recruit 294 couples into the proposed study (~8 couples/month). Our main recruitment strategy will be through the Oregon State Cancer Registry. We have used OSCaR in previous studies allowing us to target recruitments by cancer site and proximity to exercise locations. Between 50%-80% of potential participants in our prior trials are respondents from OSCaR recruiting efforts. Current records indicate that there are 2616 living persons who were diagnosed with PC, BC and CRC in Oregon, that are between the ages of 40-70 years old, within 2 years of diagnosis, and who live within a 10-mile radius of the Portland metro area. Based on our prior recruitment for our pilot of *Exercising Together* and GET FIT using OSCaR, 28% respond to recruitment letters and of those 65% were eligible and then 55% enroll, for an overall enrollment rate from the registry of 10%. Using OSCaR for the current trial would be expected to yield **261 participants**, close to our target sample size. Other strategies that we will employ are: 1) Clinician referral through OHSU Hospital and Community Oncology clinics that serve outer Portland area. Physicians referral accounted for ~15% of past enrollees and, 2) Direct community recruitment using newspaper ads, radio, web and presentations at cancer organizations and conferences, which recruited 25% of participants in our previous cancer exercise trials. Patients may also be recruited through Tuality Healthcare, or Adventist Medical Center. Additional recruitment will occur by obtaining data (name, phone number, email, address, cancer diagnosis and treatment information) from OCTRI's Cohort Discovery, OCTRI's 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.

Clinical practice head at each site will be contacted about the study and their permission will be obtained before any message is sent.

Ancillary study: Participants may also be recruited through the Oregon Office of Rural Health or the Oregon Rural Practice-based Research Network.

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 Knight Cancer Research Building to meet with the study coordinator to sign an online IRB-approved Consent Form prior to any study-related procedure. The Consent Form will describe the goals of the study, study procedures, confidentiality, risks, benefits, and voluntary nature of the research. After they view the consent online, and click the box that they have read and agree to participate (indicating that they have signed the consent), they will be sent links and requested to complete REDCap surveys. 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 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 at OHSU.

During periods of hospital recommendations for decreased in-person contact, re-consent for the 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 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.

Ancillary study: Individuals being recruited for the ancillary study 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/specimens 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/specimens released to other investigators will be labeled with only the code.

Data/specimens from this study will be banked in a repository for future use as part of this protocol. Access to data/specimens 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 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/efficacy review will occur early in the intervention

period to determine potential safety concerns or benefits of the intervention well 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 50 enrolled couples (~25% of total sample) have completed 3 months of exercise training to assess early for program safety. The efficacy review will be conducted by an independent monitor, Dr. Tomi Mori, a biostatistician and measurement expert in the OHSU Knight Cancer Institute and Oregon Clinical Translational Research Institute (OHSU's CTSA) and not a member of the study personnel, after the first 50 couples (100 participants) have completed their first post-intervention (6 month) testing appointment.

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, the home-program phone calls, 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

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial and ethnic composition of the study will include a higher proportion of African Amercian 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
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	34	34		68
Not Hispanic or Latino	260	260		520
Unknown				
Ethnic Category: Total of all subjects*	294	294		588*
Racial Category				
American Indian or Alaskan Native	4	4		8
Asian	11	11		22
Black or African American	5	5		10
Native Hawaiian or other Pacific Islander	1	1		2
White	246	246		492
More than one race	11	11		22
Unknown	16	16		32
Racial Category: Total of all subjects*	294	294		588*

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

Table 3: Projected Accrual for Ancillary Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	4	4		8
Not Hispanic or Latino	26	26		52
Unknown				
Ethnic Category: Total of all subjects*	30	30		60*
Racial Category				
American Indian or Alaskan Native	0	0		0
Asian	1	1		2
Black or African American	1	1		2
Native Hawaiian or other Pacific Islander	0	0		0

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
White	25	25		50
More than one race	1	1		2
Unknown	2	2		4
Racial Category: Total of all subjects*	30	30		60*

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

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:

The number of children with these types of cancer is limited

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