Exercise Intensity Trial (EXCITE): A Randomized Trial Comparing the Effects of Linear Versus Nonlinear Aerobic Training in Women with Operable Breast Cancer

PROTOCOL FACEPAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan Kettering Cancer Center

Participating Institutions – If multicenter study coordinated by MSK:	**PI's Name**	**Site's Role**
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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

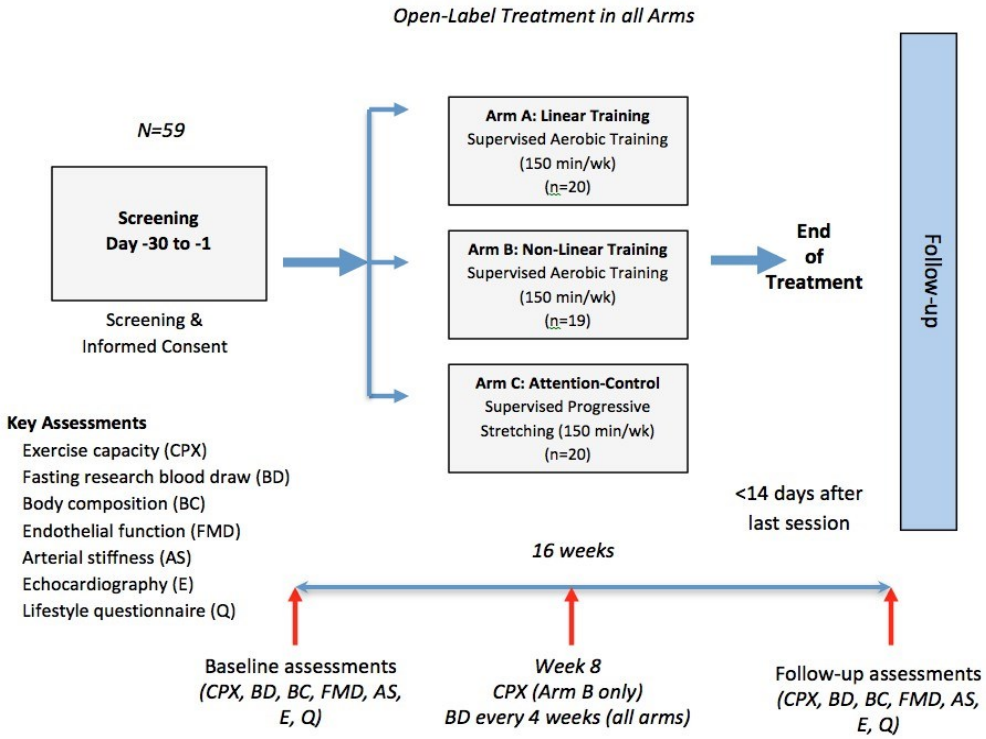
Primary Objective: To compare the efficacy of linear aerobic training versus nonlinear aerobic training, relative to progressive stretching (attention-control group), on exercise capacity (VO_{2peak}) in women with operable breast cancer following the completion of primary adjuvant therapy.

Design: A total of 174 women with histologically confirmed operable breast cancer, meeting the eligibility criteria defined in Section 6.0, will be randomized to one of the following three arms in a 1:1:1 ratio (n=59/group): **Arm A**: supervised linear aerobic training, **Arm B**: supervised nonlinear aerobic training, or **Arm C**: progressive stretching (attention-control group) (see **Figure 1**).

This randomized controlled trial (RCT) is a continuation of a clinical trial initiated and conducted at Duke University Medical Center (DUMC) in Durham, NC by the principal investigator, Lee Jones, PhD. The trial was suspended at DUMC (protocol-independent) due to change of the PI's institution. At the time of trial suspension, a total of 115 participants had been randomly allocated to three study groups: n=38 in Arm A, n=39 in Arm B, and n=38 in Arm C. Of these 115 participants, 109 successfully completed all study procedures, and 6 participants were lost to follow-up.

At MSK, 59 participants will be enrolled and randomized until the target enrollment of n=174 is met. Twenty participants will be randomized to Arm A; 19 to Arm B; and 20 to Arm C. At the end of the trial, data will be analyzed for the pre-planned target sample size (n=174).

Figure 1: Study Schema



2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Primary Objective

To compare the effects of supervised linear aerobic training versus supervised nonlinear aerobic training, relative to progressive stretching (attention-control group), on VO_{2peak} in women with operable breast cancer following the completion of primary adjuvant therapy.

2.2 Secondary Objectives

- To compare the effects on resting and exercise cardiac function;
- To compare the effects on pulmonary function;
- To compare the effects on arterial stiffness;
- To compare the effects on endothelial function;
- To compare the effects on body composition;
- To compare the effects on patient-reported outcomes (e.g., quality of life, fatigue) ;
- To collect and bank blood samples for future correlative studies; and
- To assess and compare the safety of supervised aerobic training.

3.0 BACKGROUND AND RATIONALE

3.1 Indication

The intended indication for supervised linear or nonlinear aerobic training is the treatment of impaired exercise capacity (i.e., global cardiovascular function) in patients with operable breast cancer following the completion of primary adjuvant therapy.

3.2 Background and Rationale

Exercise capacity is one of the most important indicators of health and longevity in humans.[1,2] The capacity of mammals to transport oxygen (O_2) from the atmosphere to the muscle mitochondria determines an individual's exercise capacity.[3] Maximal or peak oxygen consumption (VO_{2peak}) provides the gold standard measurement of exercise capacity and is strongly and inversely related to risk of death.[4-8]

The importance of exercise capacity following a breast cancer diagnosis has received limited attention.[9] However, over the past decade, there has been increased recognition and acceptance of the importance of therapy late effects (e.g., cardiovascular disease, type 2 diabetes, fatigue, deconditioning) as a major but underappreciated area in breast cancer management.[10] Poor exercise capacity may be of central importance for certain adverse late effects — including impaired left ventricular ejection fraction, elevated cardiovascular disease (CVD) risk profile, poor quality of life, and fatigue — following the completion of adjuvant therapy for operable breast cancer.[11-13] Further, recent landmark observational studies report that regular self-reported physical activity (e.g., brisk walking, ≥30 minutes/day, 5 days/week), a major determinant of exercise capacity, is associated with 30% to 50% reductions in breast cancer-specific mortality and all-cause mortality following the completion of adjuvant therapy.[14,15]

Despite its importance, women with breast cancer have markedly reduced exercise capacity. In a series of studies by our group, we observed that VO_{2peak} was approximately 30% below that of age-matched *sedentary* healthy women up to three years following the completion of adjuvant therapy.[11,12,16] The precise causes of the significant and marked impairments in VO_{2peak} are not known but likely are a consequence of direct cytotoxic therapy-associated injury to the cardiovascular system (e.g., impairments in the organ components that govern VO_{2peak}) together with lifestyle perturbations (e.g., deconditioning and weight gain) that we have termed the ‗multiple hit' hypothesis.[9]

A growing number of research groups have investigated the efficacy of supervised exercise training interventions (aerobic, resistance, or combination training) to counteract therapy-induced poor exercise capacity both during and following the completion of adjuvant therapy. Overall, the current literature base indicates that supervised exercise training is a safe and feasible adjunctive therapy associated with significant improvements in objective measures of exercise capacity (including VO_{2peak} as measured by a symptom-limited cardiopulmonary exercise test (CPET)) as well as a broad range of PROs.[17] Preliminary data also indicate that exercise training, particularly aerobic training, may cause favorable improvements in circulating metabolic hormone concentrations in women with operable breast cancer following the completion of adjuvant therapy.[18,19]

Although much progress has been made over the past 20 years, the format and intensity of exercise training required to induce optimal improvements in VO_{2peak} and other pertinent outcomes in women with breast cancer have not been investigated. The American College of Sports Medicine (ACSM) convened a panel of experts to review the available evidence supporting exercise prescription guidelines for cancer survivors.[20] The panel concluded that cancer patients follow the 2008 Physical Activity Guidelines for Americans (≥ 150 minutes/week of moderate-intensity, or ≥ 75 minutes/week vigorous-intensity aerobic exercise or an equivalent combination of moderate- and vigorous intensity aerobic exercise), yet few studies have tested this empiric prescription in a formal randomized controlled trial.

Moreover, the most important methodological consideration when conducting any exercise training trial is that the exercise prescription closely adheres to the fundamental principles of training (i.e., individualization, specificity, progressive overload, and rest/recovery). Alarmingly, two recent systematic reviews found that the vast majority of exercise training trials in the oncology setting did not comply with these fundamental principles.[21,22] Rather, the vast majority of trials investigate the effects of exercise training prescriptions in which the majority of training sessions are performed at the same intensity and duration; thus, training volume remains constant across the entire intervention — this is known as a linear exercise training prescription. This is problematic because as VO_{2peak} improves, the adaptation from an identical exercise stimulus diminishes; therefore, there is an insufficient stimulus to induce further physiologic adaptation.

In contrast, in nonlinear exercise training prescriptions, the intensity, duration, and occasionally, the frequency, of training sessions are sequenced in such a fashion that training volume is continually increased across the entire program (i.e., the principle of progressive overload). This approach also adds important variety to the prescription that not only continually alters the exercise ‗stress' (to optimize adaptation), but can also stimulate

participant interest and motivation. In addition, training intensity is sequenced such that higher intensity or higher volume training is followed by lower intensity (recovery) training and rest days to optimize adaptation (i.e., the principle of rest and recovery). Our group has previously demonstrated the safety, feasibility, and potential efficacy of a nonlinear exercise training approach in several cancer populations.[23-26] However, no study to date has compared whether a nonlinear exercise training approach is superior to the traditional, linear training approach in patients with cancer.

Against this background, we designed the EXCITE trial, a randomized controlled trial comparing the effects of supervised linear aerobic training versus nonlinear aerobic training in women with operable breast cancer following the completion of primary adjuvant therapy.

3.3 Effects of Aerobic Training on Exposure to Other Conventional/Novel Anticancer Therapies

There is no clinical data on the effect of aerobic training (or progressive stretching) on the therapeutic index of anticancer agents used in the management of breast cancer. Eligible subjects in this trial will not be receiving any primary adjuvant therapy, but they may potentially be receiving endocrine therapy. All clinical studies to date have focused on the effects of exercise training interventions to prevent and/or mitigate the psychosocial and/or physiological side-effects of cancer therapy; whether exercise training influences the pharmacodynamics (PD) or pharmacokinetics (PK) of anticancer therapy has not been investigated.

3.4 Effects of Conventional/Novel Anticancer Therapies on Aerobic Training

Our group, as well as others, have demonstrated that different forms of anticancer therapy cause unique and varying degrees of damage to various components of the cardiopulmonary system (heart-lung-blood-muscle axis). Collectively, these effects lead to significant and marked declines in global cardiopulmonary function, manifest as poor exercise tolerance (decreased VO_{2peak}). A major rationale for this trial is to determine the optimal aerobic training prescription approach to reverse this phenotype in women with operable breast cancer.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This open-label, three-arm randomized controlled trial will compare the effects of supervised linear aerobic training versus supervised nonlinear aerobic training, relative to progressive stretching (attention-control group), in women with operable breast cancer following the completion of primary adjuvant therapy. The primary endpoint is VO_{2peak}, as measured by a symptom-limited cardiopulmonary exercise test (CPET).

The study periods will include screening, study intervention, and follow-up assessments.

4.3 Intervention

Following eligibility confirmation participants will be randomized to one of three study arms. All participants will undergo their first aerobic or stretching training session at MSK within a maximum of 14 days following randomization.

Participants will perform structured supervised aerobic training as part of clinical trial participation. Exercise performed outside the structured sessions (i.e., contamination) will be assessed via self-report of exercise behavior. For ethical reasons, we will not instruct participants not to exercise outside the structured sessions, but we will encourage participants to maintain their level of exercise behavior prior to the initiation of the trial.

At Weeks 4, 8, and 12, all participants will perform a fasting research blood draw. Participants assigned to the nonlinear aerobic training (Arm B) will also perform a CPET at midpoint. The purpose of this test is to re-assess exercise capacity to re-prescribe aerobic training to ensure progressive cardiovascular adaptation across the entire intervention period.

4.4 Future Use of Samples

Following the completion of the trial, banked samples will be used for future correlative studies to evaluate the effects of different aerobic training prescriptions, relative to control, on blood-based biomarkers. Specific biomarkers of interest include metabolites and cytokine and angiogenic factors. A material transfer agreement (MTA) will be instituted before any samples are transferred.

Any projects outside of the scope of this protocol will need to be approved by the IRB/PB. A biospecimen correlative protocol detailing the proposed project will need to be approved by the IRB/PB prior to the start of the project.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

There are no therapeutic agents in this trial.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Aged 45–80 years
- Female
- Has been diagnosed with early-stage breast cancer
- Post-menopausal, defined as:
    - Age ≥ 45 with no menses for at least 2 years
    - Chemically induced menopause through ovarian suppression, as determined by the primary oncologist
- An interval of at least one year, but no more than five years, following the full completion of primary therapy for malignant disease. Primary therapy is defined as:
    - Surgery plus radiation
    - Surgery plus chemotherapy
    - Surgery plus trastuzumab
    - Surgery plus hormone therapy

Note: For patients who receive hormone therapy following surgery, the definition of one-year post-completion of therapy is defined by the surgery date. Patients who are currently receiving hormone therapy are eligible for enrollment.

- Weight of <205 kgs
- ECOG status of 0 or 1
- Life expectancy ≥ 6 months
- Performing less than 150 minutes of structured moderate-intensity or strenuous intensity exercise per week.
- Exercise intolerance, defined by a VO_{2peak} below that predicted for active age- and sex-matched individuals (**see Appendix H).**
- Willing to be randomized to one of the study arms
- Able to complete an acceptable baseline CPET, in the absence of high risk ECG findings or other inappropriate response to exercise as determined by the investigator.
- Able to achieve an acceptable peak baseline CPET, as defined by any of the following criteria:
    - Achieving a plateau in oxygen consumption, concurrent with an increase in power output;
    - A respiratory exchange ratio ≥ 1.10;
    - Attainment of maximal predicted heart rate (HR_{max}) (i.e., within 10 bpm of age-predicted HR_{max} [HR_{max} = 220-Age[years]);
    - Volitional exhaustion, as measured by a rating of perceived exertion (RPE) ≥ 18 on the BORG scale (**see Appendix E**)

6.3 Subject Exclusion Criteria

- Any of the following absolute contraindications to cardiopulmonary exercise testing:
    - Acute myocardial infarction within 3–5 days of any planned study procedures
    - Unstable angina
    - Uncontrolled arrhythmia causing symptoms or hemodynamic compromise
    - Recurrent syncope
    - Active endocarditis
    - Acute myocarditis or pericarditis
    - Symptomatic severe aortic stenosis
    - Uncontrolled heart failure
    - Acute pulmonary embolus or pulmonary infarction within 3 months of any planned study procedures
    - Thrombosis of lower extremities
    - Suspected dissecting aneurysm
    - Uncontrolled asthma
    - Pulmonary edema
    - Respiratory failure
    - Acute non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)
- Presence of any other concurrent, actively treated malignancy
- History of any other malignancy treated within the past 3 years (other than non-melanoma skin cancer)

- Presence of metastatic disease
- Room air desaturation at rest ≤ 85%
- Mental impairment leading to inability to cooperate.
- Any other condition or intercurrent illness that, in the opinion of the investigator, makes the participant a poor candidate for the trial

7.1 RECRUITMENT PLAN

Potential participants will be identified by a member of the patient's treatment team, the protocol investigator, or members of the Exercise-Oncology Research Program (Ex-Onc) at Memorial Sloan Kettering Cancer Center (MSK). If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential participants contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator and Ex-Onc research staff may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSK in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective participant will be conducted either by the treatment team, investigator, or the Ex-Onc research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential participants; and (4) maintaining information in a screening log of patients approached (if applicable).

Two strategies will be employed for participant recruitment:

1. Mail-Based Recruitment: Ex-Onc research staff will obtain from DataLine a list of potential participants meeting basic eligibility criteria.

   Ex-Onc research staff will contact the potentially eligible patient's primary attending physician to confirm the patient's current status and to seek approval to send the patient a mail-based letter of introduction (**see Appendix B**) and a copy of the consent form. The letter of introduction will be signed by the protocol PI. Patients interested in trial participation will be directed to call the Ex-Onc office to ask any questions they may have, receive further instructions, and discuss next steps. To further assess eligibility of potentially eligible patients, the GLTEQ will be administered by phone. Patients meeting all study requirements will be scheduled for a baseline protocol appointment. Patients will have the opportunity to review the written consent form prior to completing any tests or procedures during the baseline protocol appointment. The patient will sign the consent form at this visit.

   Patients not responding to the mailed letter of introduction within two weeks will be sent a second mailing. Patients still not responding a few weeks after the second mailing will be contacted by telephone by Ex-Onc personnel to gauge patient interest in trial participation. One additional phone call may be made to the patient, if needed. The study team will not make more than four total attempts (mailings and phone calls) to contact a patient.

2. Clinic-Based Recruitment: Potentially eligible patients attending a scheduled clinic visit with their primary attending oncologist at the Breast and Imaging Center (BAIC) will be approached at that visit. Patients may also be given a brochure at this visit with their oncologist as an introduction to the program. Ex-Onc research staff will obtain primary attending oncologist approval prior to or in conjunction with approaching any patient about trial participation. This initial encounter will include a discussion of the proposed trial, proposed treatments, and the rationale for use. Interested patients will answer questions from the GLTEQ to assess eligibility. Eligible patients interested in trial participation will have the opportunity to review and sign an informed consent during this clinic visit.

Following the initial consultation, interested participants will be contacted by telephone by Ex-Onc research staff to schedule the baseline assessment visit. Minorities and women are well-represented in the Breast Medicine clinics, and we anticipate appropriate representation in the trial accrual.

7.1 Blinding

This study is open label. Due to the nature of aerobic training interventions, participants, exercise physiologists, investigators and Ex-Onc research staff cannot be blinded to arm allocation.

7.2 Study Duration

The total duration of the study for each participant will be a maximum of 17 weeks. Participants may receive study interventions for a maximum of 16 weeks, unless study

treatment is discontinued. Patients will be followed for up to one year following the last patient visit.

8.0 PRETREATMENT EVALUATION

8.1 Screening Period

The screening period consists of initial patient review, informed consent and GLTEQ. The GLTEQ is used to measure a persons current level of physical activity in terms of the duration and type of exercise. Ex-Onc research staff will maintain a screening log for all potential study participants. Each consented participant will be assigned a screening identification (Study ID) number in consecutive numerical order, beginning with 001.

Patients consented who do not subsequently meet eligibility criteria will be registered as ineligible. If research samples have been collected on those patients they will be discarded in accordance with regulations.

A new Study ID number will be assigned to a participant who is rescreened after originally failing to meet study eligibility.

8.2 Baseline Study Assessments

Participants will complete a symptom-limited CPET before undergoing all other baseline assessments. The baseline study assessment period will take place within 30 days of registration, except where otherwise noted.

Within 30 days of registration all participants will undergo the following baseline assessments:

1. Fasting research blood draw;
2. Fasting, non-invasive measurement of regional arterial stiffness (AS) and flow-mediated dilatation (FMD);
3. Resting assessment of left ventricular function using echocardiography;
4. Symptom-limited CPET with 12-lead ECG and pulmonary function testing;
5. Post-VO_{2peak} echocardiography;
6. Lifestyle questionnaire (**see Appendix A**); and
7. A dual-energy X-ray absorptiometry (DEXA) scan to assess body composition.

The completion of these assessments will take approximately 3 to 4 hours and will be conducted in the Ex-Onc Integrative Physiology Laboratories at Memorial Hospital (in Cardiology), the Rockefeller Outpatient Pavilion at 53rd Street (in Cardiology), or the Sidney Kimmel Center for Prostate and Urologic Cancers. Participants will be given an opportunity to eat a light snack following their fasted assessments. Participants will be encouraged to bring their own snack; however, the Ex-Onc team will also have extra snacks, such as granola bars, available in case participants do not bring their own.

At the baseline visit, participants will also receive a welcome packet (**Appendices C, D, F**), which contains information about the program and an easy-to-use study calendar.

The DEXA scan will be performed at either the BAIC or the Rockefeller Outpatient Pavilion.

To maximize internal validity, we will try to schedule study endpoint assessments in the same order as they were completed at baseline, midpoint and followup.

All baseline study assessments are described in **Table 1**.

Table 1. Baseline Study Assessments

REQUIRED ASSESMENT	DESCRIPTION
Resting left ventricular function by 3-dimensional echocardiography (3DE)	Three-dimensional transthoracic echocardiograms will be performed by experienced sonographers and acquired with commercially available equipment (Vivid 7 or E9, GE Healthcare, Milwaukee, WI). Following completion of the 2DE, a full volume dataset will be acquired using a matrix array transducer with gated 4 beat acquisitions for assessments of left ventricular (LV) volumes by 3DE. A 3DE acquisition of the entire LV will be generally performed in <10 seconds. All assessments will be stored digitally for offline analyses performed using EchoPAC PC workstation (version BT11, GE Medical, Milwaukee, WI). Conventional 2D measurements of LV dimensions, Doppler, and diastolic function parameters will be performed and averaged over 3 cardiac cycles according to American Society of Echocardiography guidelines.[29-31] Left ventricular volumes and left ventricular ejection fraction (LVEF) by 3DE will be determined by manipulating the full volume dataset to derive conventional apical 4-, 3-, and 2-chamber views using TomTec offline analysis software (4D LV-Function, Unterschleisheim, Germany). After selection of reference points, a 3D endocardial contour will be automatically generated and manual adjustment will be performed as necessary. The resultant end-diastolic (EDV) and end-systolic volumes (ESV) will be used to calculate LVEF.[32]
Symptom-limited CPET to assess peak oxygen consumption (VO_{2peak})	VO_{2peak} will be evaluated using an electronic motorized treadmill test with 12-lead ECG monitoring (Mac® 5000, GE Healthcare) performed by certified exercise physiologists. CPET provides assessment of peak oxygen consumption (VO_{2peak}). Expired gases will be analyzed continuously by a metabolic measurement system (Parvo Medics TrueOne 2400). During the test, participants will begin walking on a treadmill at a participant-specific designated speed and grade for approximately 2 minutes. The speed and/or grade will then be increased every 1–2 minutes until exhaustion or a symptom-limitation is reached. During exercise, oxyhemoglobin saturation will be monitored using finger pulse oximetry, while blood pressure will be measured manually by auscultatory sphygmomanometer every two minutes (± 1 minute).

	The CPET may be terminated at the discretion of the exercise physiologist if abnormal ECG findings or abnormal response to exercise is observed, or if acceptable test criteria are not met.
Post VO_{2peak} left ventricular function by 2-dimensional echocardiography (2DE)	As soon as possible following completion of the CPET, participants will be placed in the supine position and 2DE grayscale images will be obtained in the apical 4-, 3-, and 2-chamber views. Wall motion scoring index (WMSI) will be calculated at rest and post-exercise using the 17 segment model by adding the individual segment scores (1 = normal; 2 = hypokinesia; 3 = akinesia; 4 = dyskinesia) and dividing by number of segments scored.[29] 2D LV volumes and LVEF will be calculated offline using the modified Simpson's biplane method. Cardiac output will be calculated as the product of LV stroke volume and heart rate, indexed to body surface area (BSA).
Pulmonary function testing	Pulmonary function will be determined using standard spirometry. All measures will be performed in a sitting position according to the American Thoracic Society guidelines.[36]
Regional arterial stiffness	Conduit regional artery stiffness of the entire aorta will be assessed non-invasively by measuring carotid-femoral pulse wave velocity (PWV) using 2 hand-held tonometers (SPT-301 Millar Instruments, Houston, TX). Carotid and femoral artery waveforms will be recorded simultaneously with the mechanotransducers directly applied to the skin over the greatest area of pulsation. Twenty consecutive reproducible beats will be collected simultaneously at both sites, with a concurrent electrocardiograph to obtain R-R intervals. Pulse transit time will be determined as the difference in time from R interval to systolic upstroke at each location. Systolic upstroke will be determined by identifying the foot or —notchll of the blood pressure waveform. This will be done by applying a band pass filter between 5-30 Hz, selecting the minimum value of the filtered signal. Pulse distance will be determined using anthropometric measuring tape subtracting the distance from carotid measurement to sternal notch from the distance from sternal notch to femoral pulse measurement. This method has been shown to be the optimal non-invasive measurement compared to invasive measure. PWV will then be determined by taking the pulse transit time/distance.
Flow-mediated dilatation (FMD) to assess endothelial function	Peripheral artery flow-mediated dilatation (FMD) will be performed on one arm with the subject in a supine position with the forearm extended and slightly supinated. A rapid inflator blood pressure cuff will be placed on the forearm just distal to the antecubital crease and the brachial artery will be imaged using high-resolution B-mode ultrasound and a 7.5MHz linear array transducer (Terason, t3200). Ten-second r-wave triggered digital clips (artery diastole) will be captured at baseline (following 10min of supine rest), during five minutes of forearm occlusion, and a 120 sec r-wave triggered digital clip will

	be captured beginning at cuff deflation (hyperemia) as previously described.[37] Offline analysis using specialized software (Brachial Tools, Medical Imaging Applications, Illinois) will permit for identification of peak dilation and dilation at specific pre-specified time points (60, 120 sec).[37]
Dual energy x-ray absorptiometry (DEXA) to assess body composition	Body fat percentage, and lean and fat body mass will be assessed by dual energy x-ray absorptiometry using a Lunar Prodigy multiple detector fan-beam densitometer (GE Medical Systems, Madison, WI). After calibration with an anthropomorphic phantom, single-beam, whole-body scanning will be employed on supine-positioned subjects. Data will be obtained from each scan for fat and lean body mass expressed to the nearest tenth of a gram (and percent) for the total body region, as well as in defined body zones (e.g., legs, trunk and arms). In the two hours prior to the DEXA scan, participants will be asked to avoid a large meal, avoid caffeine, avoid alcohol, and avoid tobacco. Participants will also be instructed to avoid strenuous activity for at least twelve hours before the scan. Efforts will be made for baseline and follow up DEXA assessments to be performed on the same machine.
Patient-reported outcomes (via Lifestyle Questionnaire, Appendix A)	Patient-reported outcomes will be assessed using a patient-administered questionnaire to assess quality of life, fatigue, pain, and sleep quality. • *Quality of Life (QOL)* will be assessed by the Functional Assessment of Cancer Therapy–Breast (FACT-B) scale developed for the assessment of patient symptoms and QOL in breast cancer patients.[38] • *Fatigue* will be assessed using the 13-item FACIT-Fatigue scale for the assessment of fatigue in cancer patients.[39] • *Pain* will be assessed using the 10-item Brief Pain Inventory (BPI) which was designed to measure multiple clinically relevant aspects of pain such as pain intensity and interference from pain in cancer populations.[40] • *Sleep Quality* will be assessed by the Pittsburgh Sleep Quality Index (PSQI).[41] • *Medical Outcomes Trust Short Form Health Survey (SF-36):* The SF-36 is a psychometrically robust self-report questionnaire that measures general health-related quality of life in 8 domains of health: physical functioning (SF-36 PF), role limitations caused by physical health (role-physical), bodily pain, general health perceptions, vitality, social functioning, role limitation due to emotional problems (role-emotional) and mental

	health.[42]
Complete Blood Count (CBC), Glucose and Lipid Panel	Blood will be drawn per clinical practice and analyzed by MSK Clinical Chemistry.
Fasting research blood draw	Blood collection should take place prior to the initiation of any study related interventions, whenever possible.

Following the completion of all baseline assessments and final confirmation of eligibility, participants will be randomized to one of the three study arms.

Participants who do not meet eligibility criteria will be informed of their status and considered a screen failure.

9.1 TREATMENT/INTERVENTION PLAN

9.2 Study Assessments Visit Windows

Testing slots and procedure availability must be taken into consideration when scheduling study follow-up visits. Visits may be split across the window to permit for completion of all study-related assessments.

9.3 Evaluation Prior to Initiation of Intervention

Prior to the initiation of each intervention session participant resting vital signs will be assessed as per **Appendix H** to ensure the participant can safely proceed with the session. The planned session will not be initiated if the exercise physiologist observes any concerns that may compromise participant safety and/or the integrity of the planned session.

9.4 Study Interventions

The study interventions are supervised linear aerobic training (Arm A), supervised nonlinear aerobic training (Arm B), or progressive stretching (attention control) (Arm C). All sessions will be performed in a supervised setting by a Ex-Onc exercise physiologist. Sessions will take place at the Sidney Kimmel Center for Prostate and Urologic Cancers or Sillerman Center for Rehabilitation.

All aerobic training sessions will be prescribed by an exercise physiologist under the direction of the Program Director. All exercise physiologists are trained in either Basic or Advanced Cardiovascular Life Support (BLS/ACLS).

Participants will be instructed to adhere to fasting guidelines for food, caffeine, tobacco, alcohol and exercise as outlined in Appendix H.

All sessions, regardless of randomization arm, will include a warm-up. The aerobic arms, A and B, will also include a cool-down. Heart rate, oxygen saturation and blood pressure will be

assessed prior to and following each intervention session. All adjustments to the intervention sessions will be implemented according to the standard care procedures of the exercise physiologists and will be source documented.

9.3.1 Arm A — Linear Aerobic Training

The ultimate goal is for participants to complete approximately 130–180 minutes/week of aerobic training, at 60% to 75% of the individually determined exercise capacity (VO_{2peak}), for 16 weeks. VO_{2peak} will be determined by the second CPET performed at baseline. The weekly exercise will be achieved via either 3 to 4 individual aerobic training sessions (**see Appendix H**). All sessions are required to be supervised. Intensity and duration of aerobic training is prescribed and is implemented in accordance with standard exercise training principles. This approach will be applied to guide each participant's prescription, with dose and scheduling modifications made by exercise physiologists, as required.

9.3.2 Arm B — Nonlinear Aerobic Training

The ultimate goal is for participants to complete approximately 130–180 minutes/week of aerobic training at 55% to 100% of the individually determined exercise capacity (VO_{2peak}), for 16 weeks. VO_{2peak} will be determined by the second CPET performed at Baseline, as well as the CPET performed at midpoint. The weekly exercise will be achieved via 3 to 4 individual aerobic training sessions (**see Appendix H**). All sessions are required to be supervised. Intensity and duration of aerobic training is prescribed and is implemented in accordance with standard exercise training principles (e.g., in a progressive manner with planned recovery between high-intensity sessions). This approach will be applied to guide each participant's prescription, with dose and scheduling modifications made by exercise physiologists, as required.

9.3.3 Arm C — Progressive Stretching Group (Attention control)

The ultimate goal for the progressive stretching program is 3 to 4 individual stretching sessions (**see Appendix H**). All sessions are required to be supervised. Duration of the stretching sessions is prescribed and implemented in accordance with standard stretching and flexibility training principles. This approach will be applied to guide each participant's prescribed stretching plan, with dose and scheduling modifications made by exercise physiologists, as required.

9.4 Early Termination of Intervention Sessions (Aerobic and Stretching)

All intervention sessions will be immediately terminated if, at any time during a session, any adverse clinical signs and symptoms that will not allow the intervention to proceed safely are observed by the exercise physiologist. Determination of whether it is safe for the intervention to resume in the same session — for example, if the signs and symptoms are sufficiently subsided by a rest period — will be determined by the exercise physiologist.

In the event of a session termination, the appropriate medical follow-up and clearance will be performed as per post-training clearance criteria specified in the —Training Session Criteriall section of Appendix H. All signs and symptoms that result in session termination will be

source documented and reported as an adverse event to the study intervention. Future planned training sessions will continue at the discretion of the PI.

9.5 Intervention Session Dose Modification (Aerobic and Stretching)

Vital signs will be monitored during intervention sessions to ensure participant safety. Vital sign changes that are outside the expected range of the intervention will be monitored by the exercise physiologist. The exercise physiologist will use clinical discretion to determine if a modification to the prescription or termination of the session is required.

All modifications will be source documented and recorded in the study database, including the modification reason, how the session was modified, and clearance obtained, as appropriate.

Participants requiring consistent modification of the planned prescription will be reviewed by the study PI and exercise physiologists to determine appropriate action (e.g., early study withdrawal, physiological re-evaluation).

Final determination of the intensity and duration of the session against the planned session goals will be conducted by the supervising exercise physiologist following the session and will be source documented.

9.6 Study Intervention Continuation/Interruption

If a session is missed or interrupted for an adverse event (AE), the participant will be treated for the AE as per the discretion of the attending oncologist and/or PI, as appropriate. The participant will resume the intervention only after clearance from the PI.

Participants with treatment interruptions lasting longer than 4 consecutive weeks will be discontinued from the trial. In addition, any participant who misses a cumulative total of 8 weeks of the study intervention will be discontinued from trial participation. When appropriate, study follow-up assessments will still be performed.

When intervention sessions are resumed, the dosing will be progressively increased until the planned prescription can be safely resumed, according to the Ex-Onc Exercise Physiology standards of care and/or at the discretion of the Program Director.

Participants will be allowed to ‗make up' missed sessions within the 16-week study window. Participants are not allowed to *a priori* ‗bank' aerobic training sessions.

Participants experiencing disease recurrence will be removed from study.

9.7 Study Intervention Attendance and Compliance

Attendance is calculated as the number of intervention sessions attended divided by the total number of planned sessions (i.e., 4 times/week x 16 weeks = 64). *Compliance* is calculated as the number of intervention sessions attended, as well as whether the training session dose was successfully completed (i.e., participant completed the intervention session at the

planned duration and intensity) divided by the total number of planned sessions. *Non-compliance* is defined as any intervention session requiring dose modification of either the planned intervention duration and/or intensity.

9.8 Concomitant Medications

All concomitant medications at the time of study entry will be identified through a medical chart review and recorded in REDCap. Participation in the study intervention must not impact use of concomitant medications at any stage of the study period.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All evaluations being conducted during the study intervention, including the window of time in which conduct of these tests is required, are described in the schedule of activities (Table 2). Further details are provided within this section. Assessments which are initially completed at baseline, midpoint and follow up may be repeated at the investigators discression.

10.1 Cardiopulmonary Exercise Testing (CPET)

The midpoint CPET will take the place of one aerobic training session during Week 8 for participants in Arm B. This test is repeated at this time point to re-assess VO_{2peak} under the expectation that VO_{2peak} is likely to have changed in the first 8 weeks of the aerobic training program. Thus, information from midpoint testing is used to re-prescribe the aerobic training prescription to ensure continual physiological adaptations across the entire study period.

This test will not be repeated in the linear aerobic training prescription group (Arm A) or the progressive stretching group (Arm C) at Week 8.

10.2 Fasting Blood Draws

At Weeks 4, 8, and 12, participants will undergo a fasting blood draw to obtain peripheral blood to assess complete blood count (CBC) and secondary endpoints. At Baseline and Study Follow-Up, participants will also undergo fasting blood draws for complete blood count (CBC), lipid panel, fasting glucose, as well as secondary endpoints. The CBC, fasting glucose, and lipid panel will be resulted by MSK clinical labs. Blood for secondary endpoints will be collected under protocol #06-107. Plasma from these research draws will be processed and stored per the Lab Manual, before shipment to a biorepository facility, KryoCal (d/b/a Kryosphere), for long-term banking.

10.3 Exercise Contamination

We will monitor the amount of exercise performed outside of the study in all study arms using subjective methods. Participants in all arms will be asked to complete the GLTEQ at midpoint and at study follow-up to report all exercise behavior performed outside the context of the exercise prescribed in the trial. This questionnaire is important to assess the degree of exercise being performed outside of the structured sessions in all arms, which may potentially contaminate study results. At the midpoint assessment, participants will be asked to report the average weekly exercise performed outside of study aerobic training sessions since study enrollment. At the follow-up visit, participants will be asked to report the average weekly exercise performed outside of study aerobic training sessions over the past 8 weeks since the midpoint assessment.

At the investigators discretion, patients may be required to repeat any of the above assessments.

Table 2. Schedule of Activities

			Training begins at Week 1	Treatment Period (16 weeks)			Training ends at Week 17
Study Period or Visit	**Screening**	**Baseline**	**Pre-Treatment**	**Monthly Follow-up**	**Midpoint Assessment**	**Monthly Follow-up**	**Study FU**
Study Week	**NA**	**-30 days[7]**	**-2 to -1**	**4**	**8**	**12**	**17**
Window (Weeks)	**NA**	**NA**	**±1**	**±1**	**±1**	**±1**	**±2**
General Activities[1]							
Informed Consent		X					
Medical History	X						
Height, Weight, BMI	X	X					X
Vital Signs	X						X
Performance Status (ECOG)[2]	X						
Concomitant Medications	X						
Randomization[3]			X				
Study-Related End Points							
Cardiopulmonary exercise test (CPET)[4]		X			X[5]		X
Resting 3D Echocardiogram		X					X
Post-exercise 2D Echocardiogram		X					X
Pulmonary function		X					X
Body composition (DEXA)		X					X
Regional arterial stiffness		X					X
Flow-mediated dilatation (FMD)		X					X
Godin Leisure-Time Exercise Questionnaire (GLTEQ)		X			X		X
Patient-reported outcomes (Lifestyle Questionnaire)		X					X
Complete Blood Count (CBC)		X		X	X	X	X
Lipid Panel & Fasting Glucose		X					X
Aerobic Training[6]				X	X	X	
Research Blood draw		X		X	X	X	X

[1] Testing slots/procedures availability must be taken into consideration when scheduling study follow-up visits. Visits may be split across the window to permit for completion of all study-related assessments.

[2] Performance status by Eastern Cooperative Oncology Group (ECOG) scoring.

[3] Randomization should be performed on or up to 2 weeks prior to Day 1, but only after eligibility is confirmed.

[4] All potential participants will perform a second CPET at baseline within 30 days of registration to account for the presence of significant, and potentially clinically important, variability in CPET procedures (VO_{2peak} measurement).

[5] CPET at Week 8 is only for those randomized to Arm B.

[6] Arms A and B only[7] Baseline assessments to be completed within 30 days of registration.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTCAE, v 4.03. Adverse clinical symptoms that occur during or immediately following intervention sessions — with the exception of the expected heart rate, blood pressure, and SpO_2 changes that are related to exercise — will be reported as adverse events. Adverse events will be reviewed by the exercise physiologist, and graded and attributed accordingly at the end of each session. Adverse events that are not resolved at the end of a session will be reviewed with the patient during the next scheduled session to assess whether or not the event is still ongoing. During the intervention phase, adverse events requiring adjustments to the two study aerobic training prescription approaches will be made according to the Ex-Onc Exercise Physiology standards of care and/or at the discretion of the Program Director.

11.1 Side Effects

Anticipated (expected) side-effects associated with a symptom-limited CPET, the two aerobic training doses, or progressive stretching include:

- Fatigue
- Myalgia
- Arthralgia
- Back pain
- Shortness of breath (dyspnea)

Unanticipated but possible side-effects that are *rare, but serious* include:

- Cardiovascular: angina, hypotension, palpitations, rebound hypertension, syncope
- Arrhythmias
- Heart attack
- Stroke

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Primary Study End Point

Exercise Capacity (VO_{2peak}): As described in Table 1, VO_{2peak} will be evaluated using an electronic motorized treadmill CPET test with 12-lead ECG monitoring (Mac ® 5000, GE Healthcare).

Due to the presence of significant, and potentially clinically important, variability in CPET procedures (VO_{2peak} measurement), all potential participants will perform a second CPET at baseline to account for potential learning effects and variability.[35] If both the first and second CPET achieve acceptable test criteria, results of the second test will be used in all protocol procedures and statistical analyses.

12.2 Secondary Study End Points

- Resting left ventricular function by 3-dimensional echocardiography (3DE): Three-dimensional transthoracic echocardiograms will be performed by experienced sonographers and acquired as outlined in Section 8, Table 1.

- *Pulmonary Function* will be determined using standard spirometry. All measures will be performed in a sitting position according to the American Thoracic Society guidelines.[36]

- *Post-exercise VO_{2peak}:* Post-exercise VO_{2peak} and left ventricular ejection fraction (LVEF) will be assessed via 2-D echocardiography. Images will be obtained as described in Section 8, Table 1.

- *Regional Arterial Stiffness:* Assessment of arterial stiffness will be completed as described in Section 8, Table 1.

- *Flow-mediated dilatation (FMD)*: Endothelial function will be evaluated by peripheral artery flow-mediated dilatation. FMD will be performed on the left arm, as described in Section 8, Table 1.

- *Body Composition*: Body composition, including body fat percentage, fat mass, and lean body mass, will be assessed by DEXA using the methods described in Section 8, Table 1.

- *Patient-Reported Outcomes:* Patient-reported outcomes will be assessed using a patient-administered Lifestyle Questionnaire (**see Appendix A**) to assess quality of life, fatigue, pain, and sleep quality.

    - *Quality of Life (QOL)* will be assessed by the Functional Assessment of Cancer Therapy–Breast (FACT-B) (version 4) scale. The FACT-B contains 37-items, divided into four primary subscales for physical well-being (7 items), functional well-being (7 items), emotional well-being (6 items), and social/family well-being (7 items) that comprise the FACT–General (FACT-G) scale, in addition to a breast cancer subscale (10 items). The five subscales will be summed to obtain the FACT-B score (for a total score of 148).[38] We will also compute the FACT-G score (27 items, excluding the breast cancer subscale; total score of 108). All items are rated on a 0 to 4 Likert scale, using the following response format: 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much. Respondents are asked to respond to each question as it applies to the past 7 days. Higher scores on the FACT-B indicate higher QOL. Internal consistency for the FACT-G and FACT-B is well established.

    - *Fatigue* will be assessed using the 13-item FACIT-Fatigue scale for the assessment of fatigue in cancer patients.[39] Items are scored on a 0 to 4 Likert scale, as follows: 0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much. Respondents are asked to respond to each question as it applies to the past 7 days. Higher scores on the FACT-fatigue indicate better quality of life. Internal consistency for the FACIT-Fatigue is well established.[39]

- *Pain* will be assessed using the 10-item Brief Pain Inventory (BPI) which was designed to measure multiple clinically relevant aspects of pain such as pain intensity and interference from pain in cancer populations.[40] The BPI assesses for the presence of pain, pain intensity (i.e., worse, least, average, current) and functional interference from pain (i.e., activity, mood, walking ability, normal work, relations with others, sleep, and life enjoyment). It also catalogues the types of pain medications being used, and the percentage of pain relief obtained from medications.

  The BPI uses a mixture of item types. Items 1-3 querying about the presence of pain is a dichotomous —yes‖, —no‖. Items 4-7 (intensity items) utilize a 0 (no pain) to 10 (pain as bad as you can imagine) 11-point rating scale. Item 8 (percentage of pain relief) ranges from 0% (no relief) to 100% (complete relief). Item 9 inquires about the effectiveness of pain medication (as appropriate). Item 10 (a-g) inquires about interference using an 11-point numeric rating scale. Each item ranges between 0 (does not interfere) to 10 (completely interferes). Respondents are asked to respond to each question as it applies to the past 7 days. While some of the items represent single item values, pain intensity, indexed by the —Pain Severity Score‖ is calculated by obtaining the mean of the 4 pain intensity items. The Pain Interference Score is obtained by calculating the mean of the 7 interference items. The —Pain Severity Score‖ has a maximum value of 10 (i.e., —pain as bad as you can imagine‖ and a minimum value of 0 (i.e., —No pain‖). The Pain Interference Scale similarly has a maximum value of 10 (i.e., —Completely Interferes‖) to 0 (i.e., —Does not Interfere‖). Internal consistency for the Pain Severity Score and for the Interference scale has been reported as being 0.85 and 0.88 respectively.[40]

- *Sleep Quality* will be assessed by the Pittsburgh Sleep Quality Index (PSQI).[41] The PSQI assesses sleep disturbance over the past month. The PSQI is a 9-item self-report questionnaire. The PSQI uses a mixture of item types. Items 1-4 are open-ended questions that query about sleep habits. All remaining items are scored on a 4-point Likert scale which range from 0 (not during the past month) to 3 (3 or more times a week). The items produce seven component scores: sleep duration, sleep disturbance, sleep latency, daytime disturbance, habitual sleep efficiency, sleep quality, and use of sleep medications. The sum of these component scores yields a measure of global sleep quality which ranges from 0 to 21. Reliability measures indicate that the PSQI generally has acceptable internal consistency (α = .80 to .85) and test-retest reliability (r = .85 to .87).[41]

- *Physical Functioning* will be assessed using the physical functioning subscale (PF) of the Short-Form (SF) 36.[42] The physical functioning subscale is a 6-item self-report questionnaire. The PF uses a mixture of item types. Item 1 queries about overall health, scored on a 5-point scale ranging from excellent to poor. Item 2 queries about limitations to normal activities of daily living including participation in vigorous and moderate activities. All items are rated on a 3-point

Likert scale from ―yes, limited a lot‖ to ―no, not limited at all‖. Item 3 queries about limitations relating to work over the past 4 weeks using a dichotomized response (yes vs. no). Item 4 queries about bodily pain over the past 4 weeks ranging from ―none‖ to ―extremely‖. Item 5 queries about pain during the normal work week ranging from ―not at all‖ to ―extremely‖. Finally, item 6 asks four statements about general health perceptions scored on 5-point Likert scale ranging from ―definitely true‖ to ―definitely false‖. The sum of item 2 yields a measure of physical functioning ranging from 0 to 20. Other items will be considered and summed as single items. Higher scores indicate higher physical functioning. The SF-36 has well established internal consistency and test-retest reliability.[42]

Safety will be evaluated by the type and prevalence of adverse events during study-related assessments as well as aerobic training and progressive stretching sessions. The type and nature of SAEs considered in this trial include unanticipated but possible adverse events associated with exercise testing or aerobic training.

13.0 CRITERIA FOR REMOVAL FROM STUDY

The primary reasons for permanent intervention discontinuation are listed in **Table 3**.

Table 3. Primary Reasons for Permanent Intervention Discontinuation

Reason	Description
Self-withdrawal (withdrawal of consent)	Participants may permanently discontinue study intervention and withdraw from the study at any time for any reason. Following study intervention discontinuation, participants should have protocol-required follow-up assessments unless the participant specifically declines further follow-up.
Adverse event or intercurrent illness	Any intolerable adverse event (associated or not associated with the study intervention) that cannot be ameliorated by the use of adequate medical intervention or that, in the opinion of the principal investigator, would lead to undue risk if study intervention were continued.
Gross non-compliance with protocol (violation)	The investigator may request permanent discontinuation of the study intervention in the event of lack of cooperation or complete noncompliance.
Disease progression	Study intervention will be discontinued upon histologically-confirmed diagnosis of invasive breast cancer or DCIS found during standard of care screening.
Lost-to-follow-up	Reasonable effort should be made to contact any participant lost to follow-up during the course of the study in order to complete study-related assessments and record outstanding data.
Death	N/A

14.1 BIOSTATISTICS

14.2 Sample Size Calculation and Justification

The power of both an overall F-test comparison for the study's primary outcome variable, exercise capacity (VO_{2peak}), among study arms is considered as part of power calculations, as well as two primary pairwise comparisons (i.e., Arm A versus Arm B; Arm B versus Arm C). The power of pairwise comparisons is computed with adjustment for multiple comparisons using a Bonferroni correction factor (α=0.05/2 = 0.025). The comparison of Arm A vs. Arm C is also of interest but is not a primary pairwise comparison.

The power estimates were calculated using the following observed/expected change in VO_{2peak} from baseline to Week 17:

- Arm A: +1.5 $mL.kg.^{-1}min^{-1}$
- Arm B: +4.0 $mL.kg.^{-1}min^{-1}$
- Arm C: 0.0 $mL.kg.^{-1}min^{-1}$

Power estimates assume the SD for the change in VO_{2peak} to be equal for all these groups (4.0 $mL.kg.^{-1}min^{-1}$) obtained from our prior work among post therapy breast cancer patients.[11,12] In accordance to the principles of intention-to-treat, 174 patients will have evaluable post-intervention follow-up providing >99% power to detect the noted difference among the three experimental groups with an F-test conducted with two degree of freedom. With 58 patients per group having evaluable post-intervention follow-up, there is 86% power to detect a 2.5 $mL.kg.^{-1}min^{-1}$ difference in VO_{2peak} between Arms A and B; and >99% power to detect a 4.0 $mL.kg.^{-1}min^{-1}$ difference in VO_{2peak} between Arm B and Arm C using a two-sided alpha of 0.025.

A final important consideration when conducting exercise RCTs is extent of exercise ‗drop-in' or contamination in Arm C. In other words, the concern is that patients assigned to attention-control may independently initiate an exercise training program which, in turn, potentially dilutes the efficacy of aerobic training on the outcomes of interest. However, we feel this is less of a concern in the present study because patients in the aerobic training arms (Arm A and B) will be provided with a personalized exercise prescription. which will be difficult to replicate without sophisticated prescription algorithms and expertise. In addition, attention control participants are also provided with a supervised attention intervention.

Nevertheless, we will carefully monitor the amount of exercise performed outside of the study in both aerobic training arms as well as the attention control group using subjective methods described in other sections of this protocol.

14.3 Primary and Secondary End Point Analyses

14.3.1 Primary End Point Analysis: The primary objective will be to compare the effects of supervised linear aerobic training (Arm A) versus supervised nonlinear aerobic training (Arm B), relative to progressive stretching (attention-control group) (Arm C), on VO_{2peak} in women with operable breast cancer following the completion of primary adjuvant therapy.

An intent-to-treat statistical analysis will be conducted. Baseline characteristics will be compared using the Fisher exact test for categorical variables or a Wilcoxon rank sum test for continuous variables. The primary end point comparison will be analyzed using a multiple regression model to test for differences among and between the study arms in VO_{2peak} from baseline to the follow-up assessment (Week 17). The regression model will include the stratification factors [i.e., treatment with chemotherapy (yes vs. no) and current treatment with endocrine therapy (yes vs. no)].

In the absence of evidence to the contrary, multiple imputation strategies for missing Week 17 VO_{2peak} data will be performed assuming data were missing at random using logistic regression. Results will be aggregated over 20 imputed sets using the variance formula by Rubin. In addition, a per-protocol analysis will be performed using a multiple regression model to test for differences among and between the study arms in VO_{2peak} from baseline to the follow-up assessment (Week 17) on the basis of exercise adherence to the supervised aerobic training sessions (<80% versus ≥80%). In the event that groups are unbalanced on medical or demographic characteristics at baseline, we will also perform a sensitivity analysis that includes these factors in the model.

14.3.2 Secondary End Point Analyses: As for the primary end point, the intention-to-treat principle will be employed for analysis of all secondary end points. Multiple regression models will be used to test for differences among and between the study arms in secondary end points from baseline to the follow-up assessment (Week 17). The regression model will include the baseline value of the end point, as well as any other baseline characteristics that are not balanced between groups. All secondary end points are continuous.

In the absence of evidence to the contrary, multiple imputation strategies for missing Week 17 end point data will be performed assuming data were missing at random using logistic regression, as described above. Again, a per-protocol analysis will be performed using a multiple regression model to test for differences among and between the study arms in secondary end points from baseline to the follow-up assessment (Week 17) on the basis of exercise adherence to the supervised aerobic training sessions (<80% versus ≥80%). Finally, we will also perform a sensitivity analysis in the event that groups are unbalanced on medical or demographic characteristics at baseline.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

Participants will be randomly allocated, on an individual basis, to one of the three study groups.

Randomly allocated participants will remain in the same group for the entire duration of the intervention (i.e., no cross-over). To ensure randomized groups are similar at baseline, patient randomization will be stratified based on prior treatment with chemotherapy (yes vs. no) and current treatment with endocrine therapy (yes vs. no). Chemotherapy causes greater reductions in VO_{2peak} relative to other types of cancer therapy (e.g., radiotherapy); thus, it is important for groups to be balanced on this factor. Similarly, current treatment with endocrine therapy is also expected to influence the effect of aerobic training on VO_{2peak} and other endpoints; thus it is important to ensure that groups are also balanced on this variable.

A permuted block design with allocation weight of 1:1:1 is used to generate the treatment assignments. Following the successful completion of all baseline assessments, Ex-Onc staff will enter randomization criteria into REDCap. Upon confirmation of stratification factors (chemotherapy treatment and/or endocrine treatment), REDCap will electronically randomize the patient.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study, and will be under the close supervision of the Clinical Research Manager and Principal Investigator in Ex-Onc. The responsibilities of the RSA include project compliance; data collection, abstraction and entry; data reporting; regulatory monitoring; problem resolution and prioritization; and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database (REDCap and CRDB). Source documentation will be available to support the computerized patient record. The principal investigator (Dr. Jones) will maintain ultimate responsibility for the clinical trial.

The study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for behavioral randomized trials; http://www.consort-statement.org/.[50]

16.2 Role of Duke University Medical Center (DUMC)

The current trial is a single-site, phase II trial comparing the effects of a standard aerobic training prescription approach versus a novel aerobic training prescription approach in women with operable breast cancer following the completion of primary adjuvant therapy. However, this trial represents a continuing effort that was first initiated at DUMC approximately 5 years ago by the principal investigator, Dr. Jones. Prior to his appointment at MSK in February 2014, Dr. Jones was a principal investigator at DUMC. During his tenure there, Dr. Jones secured a 5-year R01 grant from the National Cancer Institute to conduct the present study. During trial conduct, Dr. Jones accepted a position at MSK and hence the protocol was closed to accrual. Participants ‗on trial' completed all study-related procedures but the study was closed to new patient enrollment.

IRB correspondence: All local IRB correspondence for DUMC that is initiated after the MSK protocol is open to accrual should be submitted to MSK. This includes but is not limited to approvals for amendments and continuing reviews as noted below. All other correspondence should be submitted to the local IRB according to local guidelines.

Amendments: Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Upon receipt of MSK IRB/PB approval, Ex-Onc research staff will immediately distribute all non-expedited amendments to DUMC for submission to the local IRB.

DUMC must obtain approval for all non-expedited amendments from their IRB within 90 calendar days of MSK IRB/PB approval.

Continuing Review Approval: The Continuing Review Approval letter from the DUMC IRB and the most current, approved version of the informed consent form should be submitted to MSK within 7 days of expiration.

Document maintenance: The MSK PI and the DUMC PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

16.3 Current Status

As of September 2013, the trial status is as follows: The grant was released on 10/09/2009 and the protocol received Institutional Review Board (IRB) approval from DUMC on 03/25/2010. As of September 2013, a total of 115 patients (of a planned 174 participants; 66%) had been recruited and randomized. Of these, 106 patients (92%) successfully completed study procedures, with 9 patients lost-to-follow-up (8%). The mean adherence rate was 77% across Arms A and B, with minimal adverse events, suggesting that all intervention sessions were well-tolerated.

Additional details are available. Overall, we were pleased with the study progress at the time of trial suspension and patient self-reports of the benefits of the trial.

16.4 Proposed Plan at MSK

Following successful transition of the PI from DUMC to MSK (and establishment of a close collaborative relationship with the Breast Medicine Service under the leadership of Dr. Clifford Hudis), the goal of this continuation trial is to complete study accural as planned (i.e., accrual of the remaining 59 patients). Based on the recruitment rate prior to trial suspension at DUMC (~3.4 patients/month) and the number of patients who would potentially be eligible for the study at MSK, we estimate that study accrual will complete within ~17 months.

16.5 Data Management

All prior data collected on this protocol is securely stored and managed in a REDCap database system at DUMC under the stewardship of Pamela Douglas, MD and James E. Herndon, II, PhD. Although the trial has been closed to enrollment at DUMC, it remains open in the DUMC IRB to permit future medical chart data abstraction; Dr. Pamela Douglas is the acting PI at DUMC.

Given that this trial was developed and initiated at DUMC, we propose that DUMC remains the data management and statistical center for this trial under the direction of James E. Herndon, II, PhD (trial biostatistician). Specifically, all study-related procedures and data collected here at MSK will be entered into two systems: (1) a REDCap database on the MSK server, and (2) REDCap software at DUMC.

REDCap software is a tool that does not require client local software and can be accessed from anywhere on the Internet. The program is secured on a Duke Health Technology Services (DHTS) server. This database will be developed, and maintenance performed, with support of the School of Medicine (SOM) Duke Office of Clinical Research (DOCR). SOM's DOCR has partnered with the School of Medicine (SOM) to implement REDCap (developed by Vanderbilt's CTSA and currently used and supported by more than 1000 consortium partners). REDCap provides: 1) a stream-lined process for rapidly building a database; 2) an intuitive interface for collecting data (with data validation and audit trail); 3) automated export procedures for seamless data downloads to common statistical packages (SAS, SPSS, etc.); 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-up.

REDCap accounts are stored within the DTMI LDAP server hosted by the Duke Office of Information Technology (OIT). Authentication occurs via the OIT implementation of Kerberos. All connections to the system, both external and internal, occur over encrypted channels. Access to components of the system is role-based and can only be granted by administrators of the system. All collected information is stored on a standalone database server hosted by Duke Health Technology Services (DHTS). The database server resides behind the DHTS internal firewall and access to the server is controlled via firewall rules.

All collected data is backed up daily, both on the local server and by the DHTS enterprise backup system. Cory Ennis (919-668-8284) is responsible for managing the server for REDCap. Ceci Chamorro, in the Duke Office of Clinical Research (919-668-9262), is responsible for managing the database platform for REDCap. At the time of this submission, REDCap is on version 5.0.20.

Server location: Fitz-East Data Center (Fitzpatrick); the directory is: /var/lib/mysql_backup/
Server support: Cory Ennis, DOCR – DHTS hosts servers (919-668-8284; cory.ennis@duke.edu)

Operational support: Ceci Chamorro, DOCR (919-668-9262; ceci.chamorro@duke.edu)

Of importance, staff entering MSK participant-related data from the Ex-Onc at MSK will not be able to view or manipulate data pertaining to DUMC participants already entered into the REDCap database. Similarly, only James E. Herndon, II, PhD and Samantha Thomas, MS (trial statisticians) will have access to MSK patient data.

The consent form contains language explaining that basic MSK participant information can only be accessed by specific individuals at DUMC.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, or more frequently, as appropriate.

16.2 Data and Safety Monitoring

This protocol describes a trial which is currently registered on ClinicalTrials.gov.

The Data and Safety Monitoring (DSM) Plans at MSK were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled —Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials‖ which can be found at: *http://www.cancer.gov/clinicaltrials/patientsafety/dsm-guidelines/page1*.

The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff

education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level or risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industry sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each participant, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed with the participant. It will be reviewed that participation in this clinical trial is voluntary and that the participant may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity, including physician visits and serial cardiac monitoring. Specific guidelines for symptom management are in place to protect the study participant.

This protocol establishes operational guidance based on current ethical and legal standards for the procurement and banking of human biologic specimens for use in future biomedical research. The protocol includes an informed consent document and research authorization that meets statutory guidelines. They inform participants of the purpose of the bank, their rights in relation to it, and the safeguards in place to protect the confidentiality of their health information.

Consent process: All patients at MSK who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All participants will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in **Section 18.0**.

Potential Risks: Our eligibility criteria and screening procedures are established to exclude individuals for whom graded exercise testing, blood collection, and supervised moderate-intensity aerobic training are not appropriate. Our screening procedures begin with medical chart review to identify individuals with any condition or reasons that may prohibit study entry, followed by oncologist approval to screen/identify patients who may not be eligible for any additional reasons. Finally, in-person assessments will be performed to screen/identify patients for cardiovascular or ECG contraindications on a symptom-limited graded exercise test (CPET). This multi-gated comprehensive approach should systematically identify and screen out any individual for whom this study is contraindicated. The risks associated with trial participation are described in detail in **Section 11**.

Cardiopulmonary Exercise Testing (CPET) — Graded exercise testing carries a finite risk of adverse cardiovascular event with <1/100,000 in well individuals and 1/10,000 in clinical populations.

Blood Collection — There are some minor risks associated with a blood draw, such as bruising and/or discomfort; however, this procedure is considered to be of minimal risk.

Supervised Aerobic Training — Similar to graded exercise testing, aerobic training carries a finite risk of an adverse cardiovascular event. Under our laboratory conditions, we have not experienced any serious adverse events in five years of aerobic training across literally hundreds of cancer patients and 1,000+ hours of training. Further, all participants would have undergone a full ECG, graded exercise test prior to aerobic training, and all sessions will be supervised by a exercise physiologist.

Dual Energy X-ray Absorptiometry (DEXA) — A DEXA carries the risk of radiation exposure; the average full-body dose of radiation is 1 to 3 mrad per DEXA scan. In this study, two DEXA scans will be completed for each patient enrolled, and the total average full-body dose of radiation per patient is 3 to 9 mrad over the course of the study. Although very rare, a potential health risk associated with DEXA is subsequent induction of cancer.

There are no known risks to undergoing the other study-related assessments in this trial.

Risks of research participation: The greatest risk is release of information from health or research records in a way that violates privacy rights. MSK will protect records so that name, address, phone number, and any other information that identifies the participant will be kept private. It will be stated to the participant that the chance that this information will be given to an unauthorized individual without the participant's permission is very small.

Benefits: A behavioral treatment strategy, such as aerobic training in women with operable breast cancer who have exercise intolerance due to the direct and secondary effects of adjuvant therapy, may improve these outcomes.

It is unlikely that the research using collected biospecimens will be of any medical benefit to participants. Neither the patient nor the treating physician will be told the specific results of any research tests on the samples; except in the case of an uncovered incidental finding which may be critical to the preventive care of the participant or their family. Research using blood or tissues in this study could lead to medical and scientific products that could improve prevention, diagnosis and treatment of disease.

Costs/compensation: Participants will be charged for physician visits, routine laboratory tests, and radiologic studies required to monitor their condition. Participants will not be billed for any study-related procedures. The participant will be informed that there are no plans to provide financial compensation for use of their human biologic specimens, nor are there plans for the participant to receive money for any new products, tests, and discoveries that might come from this research. Nevertheless, all participants will be reimbursed (in the form of two $50 gift certificates) for completion of study procedures. The total amount participants may receive is $50 for the completion of the baseline assessment and $50 for completion of follow-up assessments (Week 17). A research study receipt will be used to document

participant reimbursement at each time point. A copy of the receipt will be kept in the participant's study file.

Alternatives: The alternative to this trial would be not to participate in the study and receive routine standard of care.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g., qualified monitors from MSK) and external personnel, its authorized agents, the FDA, and/or other governmental agencies may review patient records as required.

Patient safety: Participants are monitored by physicians, oncology nurses, and exercise physiologists who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and on weekends, we have a 24-hour urgent care facility for outpatients.

Voluntariness of research participation: It is stated that taking part in this study is voluntary and patients have the right to withdraw at any time. Participation in the study will not impact the clinical care patients receive.

Withdrawal: Participants may decide at a later date that they do not want identified blood and/or tissue samples to be stored for future research. If participants decide to withdraw from the study, specimens will not be used in new studies and any remaining portions of samples that have not been used for research will be used only for clinical purposes or, if requested by the participant, destroyed. When a participant withdraws from protocol, OCR/PPR should be notified immediately. The withdrawal request will be documented in CRDB and the system updated accordingly. In addition, a note documenting the participant's withdrawal must be filed in his/her EMR.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event

- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition

- Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center.

The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study, including available standard and investigational therapies. Additionally, participants will be offered an option of supportive care for therapeutic studies.
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all participants must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

1. **Appendix A**: Lifestyle Questionnaire
2. **Appendix B**: Introduction Letter
3. **Appendix C**: Welcome Letter
4. **Appendix D**: Study Timeline
5. **Appendix E**: Borg Rating Scales for Perceived Exertion, Dyspnea, and Leg Fatigue
6. **Appendix F**: Exercise Session Information
7. **Appendix H**: Exercise Physiology Guidelines