UNIVERSITY OF WASHINGTON SCHOOL OF NURSING
CLINICAL PROTOCOL

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Title of Protocol:
Investigating Various Adaptive-Training Exercise Programs for Improving Cardiorespiratory Fitness After Breast Cancer Treatment (ACTIVATE)

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ABBREVIATIONS

FHCRC	Fred Hutchison Cancer Research Center
UW	University of Washington
SoN	School of Nursing
SoM	School of Medicine
SCCA	Seattle Cancer Care Alliance
IRB	Institutional Review Board
CRF	Cardioresipratory Fitness
QoL	Quality of Life
CVD	Cardiovascular disease
VO_2	Volume Oxygen
CPET	Cardiopulmonary Exercise Testing
MRI	Magnetic Resonance Imaging
AE	Aerobic Exercise **OR** Adverse Event
RE	Resistance Exercise
IMF	Intermuscular Fat
6MWT	Six Minute Walk Test
6MWD	Six Minute Walk Distance
DSM	Data & Safety Monitoring
SAE	Serious Adverse Event

1.0 INTRODUCTION

This document is a clinical research protocol. The described study will be conducted in compliance with the IRB approved protocol, associated Federal regulations, and all applicable IRB requirements. This study is being performed in order to examine the feasibility of administering an individually tailored exercise intervention among breast cancer survivors. Specifically, we will conduct a pilot study of a 2-arm exercise intervention among breast cancer survivors with reduced cardiorespiratory fitness.

2.0 BACKGROUND

2.1 Cardiorespiratory fitness decline in breast cancer survivors

Cancer survivors experience substantial reductions in cardiorespiratory fitness. Improved cancer treatment has led to 3.8 million breast cancer survivors in the U.S. today.[1] However, this improvement is offset by an increase in cancer therapy-related morbidity and mortality.[2–4] In particular, up to one-third of chemotherapy-treated breast cancer patients, particularly those receiving anthracycline chemotherapy, experience substantial reductions in cardiorespiratory fitness (CRF) – defined by functional limitations (e.g., becoming out of breath when walking across a room).[2–5] Unfortunately, many of these women do not regain their fitness after treatment cessation. A recent study demonstrated that even treatment historically thought to be well-tolerated is associated with long-term marked impairment of cardiorespiratory fitness.[6]

This substantial loss of fitness leads to a lower quality of life (QoL) and reduces a survivor's ability to maintain activities of daily living.[2,5,7,8] Reduced cardiorespiratory fitness also increases the risk of late-occurring cardiovascular disease (CVD),[6] and in cancer survivors strongly predicts CVD mortality.[9] Thus, an increased burden of CVD in these patients adds another layer of complexity and challenges to this already vulnerable cohort. Overall reduced cardiorespiratory fitness is associated with a 3-fold increased risk of death.[6]

Cardiac and skeletal muscle composition affect CRF. The factors that increase the risk of reduced cardiorespiratory fitness in chemotherapy-treated survivors are multifaceted and extend beyond cardiac-specific factors.[10,11] Cardiorespiratory fitness is reflective of multiple organ systems, and as such is a useful metric to estimate total body health.[9] Unfortunately, it is well-documented that cancer treatment can lead to dysfunction of many organ systems, including skeletal muscles and cardiac muscles. The changes to cardiac muscles and skeletal muscle composition – known as the cardiovascular-skeletal muscle axis – are known to play a critical role in cardiorespiratory fitness.[3,12,13] A 2018 White Paper concluded that interventions to improve cardiorespiratory fitness in cancer survivors should focus on damage that occurred along this axis.[12] Thus, interventions may need to incorporate aerobic and resistance training, depending on whether treatment-induced changes occurred to both the cardiovascular system and skeletal muscles.

2.2 Intervention

Individualized interventions targeting CRF in breast cancer are needed. Past research has demonstrated the need for individually-adaptive interventions to ameliorate CRF reductions in cancer

survivors. A meta-analysis showed significant heterogeneity in the effects of exercise interventions on fitness. While across the total cohort, exercise interventions led to significant improvements among cancer survivors, approximately one-third of participants receiving an aerobic exercise intervention saw no improvements and one-quarter continued to lose fitness, which suggests a need for examining avenues beyond aerobic training for improving CRF.[14] This is particularly important for patients who demonstrated progressive fitness loss that continued to worsen even after completing exercise treatment.[14]

There is a need to develop individually-tailored interventions, particularly for the subcohort that demonstrate reductions in cardiorespiratory post-cancer treatment. This is aligned with a recent American Heart Association position paper stating that research is needed to determine the types of exercise intervention that are effective at improving fitness in cancer survivors.[15]As there is no proven strategy to improve fitness in breast cancer survivors, providers lack an evidence base to offer an 'exercise prescription' to patients, the lack of which contributes to lower physical activity in breast cancer survivors.[15]

We can glean information on the contributors to reductions in cardiorespiratory fitness from the Fick equation which states that exercise capacity is a product of cardiac output and the AVO_2 difference,[16] a measure of oxygen differential between the arterial and venous system which reflects peripheral factors, including the ability of the skeletal muscle to oxygenate. Thus, non-cardiac factors, such as skeletal muscle dysfunction, could potentially contribute to reduced cardiorespiratory fitness in breast cancer survivors. This is supported by literature indicating in particular that increased intermuscular fat negatively impacts the skeletal muscle's ability to oxygenate[17] as well as increased intermuscular fat was the predominant factor in breast cancer survivors with reduced cardiorespiratory function.[18]

As it is yet unclear whether cancer survivors would benefit most from aerobic or strength training, this study will be the first step toward designing an intervention to test whether one exercise modality has superiority over another among cancer survivors. Thus, an adaptive intervention is an ideal design to determine which type of intervention is optimal. We propose to employ an intervention in which participants who are not responding to an exercise modality are re-assigned to a combined modality, thus tailoring the exercise intervention to respond to the needs of participants.

2.3 Experience and Preliminary Work

Our interdisciplinary research team has previously implemented a lifestyle intervention in a pilot study of women at high risk of breast cancer, some of whom who were breast cancer survivors, that involved a similar focus on exercise intervention and utilized a similar recruitment plan to identify and enroll participants.[19,20] In addition, our research team has expertise in assessment of functional exercise capacity (e.g., 6-minute walk distance, cardiopulmonary exercise testing) and of body fat depots, particularly IMF and depots of abdominal adiposity using magnetic resonance imaging (MRI).[21,22]

2.4 Risks/Benefits

Anticipated risks. No serious risks are anticipated with this study. Cardiopulmonary exercise testing (CPET) may cause some fatigue and physical discomfort. Psychological discomfort, such as anxiety or apprehension, may arise for participants related to undergoing MRI and CPET. These are not seen as significant risks with levels of discomfort beyond those that they might experience during situations

outside of the study. Participants will be informed that they can stop participating in the study at any time.

Risks associated with the intervention are minimal, even for individuals with reduced cardiorespiratory fitness. However, adverse events may occur with exercise:

> *Exercise training.* The major risks of participating in this monitored program include muscle fatigue, muscle soreness, and possible joint or skeletal injury. These risks are reduced by enrolling women without contraindications to exercise modifications, proper warm-up/cool down periods, conservative exercise prescriptions and progression, and monitoring by experienced staff (including exercise physiology specialists). If experienced, exercise-related injuries are expected to be of minimal discomfort and short duration and not significantly different than what someone might experience in everyday physical activities.

The study will maintain ongoing compliance with all University of Washington guidelines surrounding COVID-19 mitigation for in-person clinical research.

All adverse events, regardless of attribution to study procedures, will be collected and recorded. Subjects will be asked in an open-ended way about the presence of any adverse events. The PI will comply with all requirements of the IRB for the reporting of safety data and adverse/serious adverse events. For more information, see the study Data & Safety Monitoring (DSM; Appendix A)

Storing all data with only a code attached will help ensure confidentiality. However, there is a potential risk of breach of confidentiality related to collection of sensitive information and participant identifiers. Following procedures outlined in Section 9.0 will minimize possible breaches of confidentiality and obtaining informed consent will limit invasion of privacy.

MRI risk management. Participants in our study will not receive gadolinium-based contrast agents for the MRI scans.

Anticipated direct benefits to participants. Participants in the intervention group may benefit from a free, semi-supervised exercise program. All physiologic measures are performed and analyzed for research purposes only; we do not plan to share findings with participants.

Individual participants' findings. Generally, individual findings will not be shared with the participant. We do not anticipate the MRI will produce any timely, clinically actionable results. If a life-threatening condition is identified through the CPET, this result will be shared with the participant.

3.0 STUDY AIMS

1. Determine the feasibility of an individually-adaptive exercise intervention among breast cancer survivors with reduced cardiorespiratory fitness through examination of recruitment rate, enrollment rate, loss to follow-up, intervention adherence, and relative dose intensity (ratio of total completed to total planned cumulative dose)

2. Examine the endpoint of (a) safety; and explore the endpoints of (b) cardiorespiratory fitness; (c) functional capacity; (d) physiologic changes; and (e) patient reported outcomes (PRO) in the intervention vs control arms.

3. Examine the endpoint of (a) safety; and explore the endpoints of (b) cardiorespiratory fitness; (c) functional capacity; (d) physiologic changes; and (e) patient reported outcomes (PRO) in the AE vs RE vs AE+RE intervention arms.

4.0 STUDY DESIGN

4.1 Description of Study

This is a pilot study of a 2-arm randomized trial with a 2:1 initial allocation to exercise intervention or waitlist control (see Appendix B for study schema). The intervention group will then be randomly assigned (1:1) to receive either a 12-week aerobic exercise (AE) intervention or a 12-week resistance exercise (RE) intervention.

At 12 weeks, the intervention group will be assessed for intervention response, defined as a ≥5% increase in 6-minute walk distance (6MWD) over baseline. Non-responders to either AE or RE will receive 12 weeks of combined AE+RE. Intervention responders will continue the exercise intervention in their current assignment, either AE or RE alone, for the additional 12 weeks.

This study will employ a waitlist control. After 24 weeks, the waitlist control group will receive a digital copy of sessions provided to the intervention arm. The control and intervention arms' schedule of evaluations will be identical across all 24 weeks of the trial.

4.2 Endpoints

4.2.1 Primary Endpoint

Intervention Feasibility: Intervention feasibility will be determined with all-cause intervention discontinuation rate, which is the proportion of all intervention participants who permanently stop the intervention prior to Week 24 for any reason.

4.2.2 Secondary Endpoint

The secondary outcomes include:

Intervention Safety

Safety: Intervention safety will be determined by reviewing and quantifying the number of adverse events (mild, moderate, or severe), serious adverse events, and by reviewing the type and severity of adverse events attributed to study procedures among each study group. See Section 8.0 for adverse event definitions and protocols.

Study Feasibility & Acceptability

Study feasibility: Study feasibility will be measured by calculating recruitment rates (proportion of enrolled participants to all individuals approached), lost to follow-up (proportion of participants who do not complete post-intervention assessments), relative dose intensity (proportion of completed to planned sessions), early session terminations (proportion of sessions ended by participant prior to completing planned duration), intervention interruptions (missing 3 or more planned sessions consecutively), attendance (proportion of attended to planned sessions), and adherence (gathered from HR/accelerometry data and self-report of exercise via questionnaires). A benchmark to determine feasibility is <40% loss to follow-up.

Intervention acceptability: Acceptability will be measured with qualitative, open-ended to assess participant experience in the intervention and gather information for improving the protocol in future studies. Of particular attention will be the tolerability of a remote, home-based exercise intervention with a semi-supervised format.

Intervention session intensity and adherence: The Rating of Perceived Exertion (RPE) scale asks respondents to rate the intensity of exercise on a 6 – 20 scale.[23] The measure has been validated for estimating both aerobic and resistance exercise exertion levels,[24] providing a standard measure across intervention modalities. Participants will record RPE after each session in order to track session intensity and completion (adherence).

Functional Capacity

Submaximal exercise capacity: Submaximal exercise capacity, also considered functional capacity, will be determined with the six minute walk test (6MWT),[26] which measures the distance a person can walk in six minutes (6MWD). A widely used measure of submaximal exercise capacity, the 6MWT will be administered at all study timepoints to evaluate intervention response.

Strength: One Repetition Maximum (1-RM) or the maximum amount of force that can be generated in one maximum effort movement, will be used to assess participant strength at each time point. A chest press machine and leg press machine will be utilized to separately estimate upper body strength and lower body strength for each participant. The 1-RM test will be administered by a trained exercise physiologist.

4.2.3 Other/Exploratory Endpoints

Cardiorespiratory Fitness

Maximal exercise capacity: This study's primary outcome is cardiorespiratory fitness (CRF). This is operationalized as maximal exercise capacity, which is ascertained by measuring peak oxygen consumption (VO_2 peak) during CPET. All CPETs will be administered by a trained exercise physiologist using the Modified Bruce protocol, an appropriate testing paradigm for people with reduced physical functioning. This procedure will estimate the VO_2 (absolute and relative to bodyweight), VCO_2, VE/VCO_2, BP, HR. Total exercise time as well as workload and peak exercise will be collected as well. Ventilatory and work efficiency/economy will be calculated. Ventilatory threshold will be determined from VO_2 – VCO_2 plot (V-Slope).

Intervention adherence (accelerometry): Participants will wear 2 devices during the study: (1) a waist-worn actigraph and (2) a wrist-worn FitBit activity monitor (Charge 4, FitBit, San Francisco, CA). The actigraph will be worn for 7-day intervals immediately prior to the baseline and endpoint assessments. In addition, participants will be asked to wear the actigraph 24-hours per day during that 7-day interval with the exception of when engaged in water activities for the duration of their intervention participation. Together, these data will be used to gauge adherence to the exercise intervention. The raw data generated from these devices will be reviewed by a trained accelerometer analyst for quality control and cleaning. Then the analyst will calculate the amount of time (in min/per day) spent in activities of low-, moderate-, and vigorous-activity. Categorization of the level of physical activity will use accepted cutpoints from the literature. [25]

Physiologic Changes

Anthropometrics: Prior to the measurement of body weight, participants will be instructed to remove heavy clothing and empty pockets of their contents. Weight will be measured to the nearest one-tenth kg with a calibrated balance beam or digital scale. Height will be measured while the participant stands without shoes using a wall-mounted stadiometer to the nearest one-tenth cm. Hip and waist circumference will be measured to the nearest one-tenth cm.

Intermuscular fat (IMF): The ratio of thigh IMF to skeletal muscle (SM) will be ascertained via MRI by trained MRI technologists (see Appendix C for the MRI protocol). Participants will undergo a screening process with the MRI technologist to ensure that eligibility criteria for MRI scans are met. Participants will then change into a hospital gown and enter the MRI scanner. In this longitudinal assessment of IMF, the MRI technologist will be instructed to match participant scan positions across time by matching the current scan position with the participant's previous scan position, recorded at the timepoint prior. MRI analysts will quantitate total and compartment amounts of muscle and adipose tissue using cross-sectional areas of thigh skeletal muscle (SM) and IMF using commercially available software. Thigh IMF area will be calculated as the number of fat pixels within the thigh musculature multiplied by the pixel surface area. The analyst will be blinded to MRI visit number, participant's prior/future MRI results, intervention group, and participant characteristics. This technique for determining muscle composition has been validated against cadaver specimens.

Abdominal depots of fat: Subcutaneous (SQ) fat and visceral adipose tissue (VAT) will be assessed via abdominal MRI (see MRI Protocol in Appendix C). For analysis, fat depots will be separated into abdominal SQ fat and VAT which will be further segmented into intraperitoneal (IP) and retroperitoneal (RP) fat using commercially available software. SQ fat will be defined as the fat outside the muscular abdominal wall; IP fat as fat within the mesentery and omentum bounded anteriorly and laterally by the abdominal wall and posteriorly by a curved line drawn between the kidneys; RP fat as the remaining fat. Adipose tissues will be segmented and colored from other tissues based on pixel intensity and known divisions of tissue planes. The MRI analyst, blinded to participant characteristics, will correct any misidentified fat or non-fat regions using manual tools provided within the software. To calculate each of the compartmental fat deposits, the number of subpixels within each fat compartment (SQ, VAT, IP, and RP) will be multiplied by the individual pixel dimensions within the image and by the slice thickness to determine the area of fat (in cm^2) for each compartment.

Patient Reported Outcomes

Quality of Life

Quality of life will be assessed with the Short Form Health Survey-36 (SF-12), a widely used self-report measure of quality of life and health status.[27] Comprised of 12 multiple choice questions, the SF-12 queries general perceptions a participant has about their health, as well as limitations to physical activity, physical health problems, mental health problems, pain, and energy/fatigue. The SF-12 is used across health research domains, and in breast cancer has been utilized as a longitudinal monitor of quality of life.[28–30]

Physical activity: The Stanford 7 Day Physical Activity Recall (PAR) interview[31] will be used to estimate participant engagement in physical activity for the 7 days prior to each clinic visit. The PAR assesses the amount of moderate to vigorous PA performed by participants in the preceding week, as well as the amount of time completing both strength and flexibility exercises and hours of sleep each night. The PAR interview has been widely validated and previously used to assess PA outcomes in a home-based exercise intervention for breast cancer survivors.[32]

Sedentary behaviors: Time spent engaging in sedentary behaviors will be measured with the self-administered Sedentary Behaviors Questionnaire (SBQ).[33,34] The SBQ measures the minutes spent participating in 9 different sedentary behaviors per "typical" weekday and weekend day.

Perceptions of Physical Activity: Participant perceptions of their readiness for physical activity and barriers to successful PA will be captured with an internally developed scale created by combining questions assessing Capability, Opportunity, and Motivation (COM-B) for physical activity[35] and questions assessing perceived barriers to PA that have previously been used in adult cancer survivors.[36]

Perceived well-being: Participants' perception of their current well-being will be assessed with the 28-item 5-point Likert scale Functional Assessment of Cancer Therapy (FACT)-General.[37] The FACT-G contains 4 subscales measuring physical, social, emotional, and functional well-being and has been validated for reliably measuring well-being in cancer patients.[38,39]

Insomnia: Participant sleep will be assessed with the Insomnia Severity Index (ISI).[40] The ISI is a 7-item, 5-point Likert scale self-report scale measuring the nature, severity, and effects of insomnia over the previous month. Items are summed to a total score where greater than 7 indicates clinically significant insomnia.

Mood disturbances: Symptoms of anxiety and depression will be assessed with the 4-item, 5-point Likert scale Patient Health Questionnaire (PHQ-4). The PHQ-4 is a brief and validated screener for clinically significant insomnia and depression, and has been used to predict long term physical activity levels in breast cancer survivors.

Fatigue: The Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale is a 13-item scale originally developed for and widely used to assess cancer-related fatigue.[41,42] The FACIT-Fatigue scale measures severity (e.g.., "I feel fatigued"; "I feel weak all over") and impact of fatigue (e.g., "I need help doing my usual activities"; "I have to limit my social activity because I am tired") over the past week, with responses scored on a 5-point scale, from 0 "not at all" to 4 "very much." The FACIT-Fatigue scale has excellent psychometric properties and a focus on physical aspects of fatigue.

4.3 Study Procedures

4.3.1 Recruitment

This project will recruit 30 study participants through a multi-pronged approach:

Seattle Cancer Care Alliance (SCCA) clinics: At SCCA, we will work with the breast oncology clinic research team to obtain a list of potentially eligible research participants that will include patient name, phone number, and mailing address. This eligibility will be based on age and approximate end date of chemotherapy or Herceptin therapy. Potentially eligible participants identified through SCCA will receive a mailed letter endorsed by their oncologist inviting them to call the study coordinator for more information and/or screening. The study team may follow up proactively with a phone call no less than two weeks after sending the letter.

Breast cancer support groups in the community: Study information will be provided to breast cancer support groups in the community by sharing study flyers (paper, electronic, or Web versions) with the organizers of these groups and by giving presentations at in-person group events, as permitted by organizers.

Re-contacting previous breast cancer research participants: The pool of previous breast cancer research participants will be generated from past projects under the purview of the study's principal investigators or shared from affiliate investigators. Previous participants or candidates will be contacted via phone, email, or mailed letter, depending on what information is available to the study PIs.

The UW ITHS Leaf tool: The University of Washington's Leaf system will be used to generate an identifiable cohort of potentially eligible patients in the UW Medicine system. The study will query the database for patients who meet key eligibility criteria and who have recently visited the UW Medicine system for treatment. Candidates generated from this list will be sent a letter that describes the study and invites them to contact the study team should they be interested in participation. The study team may follow up proactively with a phone call no less than two weeks after sending the letter.

4.3.2 Screening

The study coordinator will use the screening script and questionnaire to complete screening (in-person or over-the-phone) of participant eligibility, according to eligibility criteria detailed in section 5.0. Inclusion criterion 4 (reduced CRF) will be estimated with an algorithm based on BMI, resting HR, and self-reported physical activity.[43] Eligible candidates will be given information on the consent process and sent a copy of the consent form for review prior to their baseline visit. Consent will occur at the baseline visit.

4.3.3 Informed Consent Procedures

Candidates will be guided through the written informed consent process. All eligible candidates will be provided the same informed consent. The consent forms will contain the details for all study procedures, including both intervention and waitlist control arms, and for the storage and protection of de-identified data. Participants will be provided with a copy for their records. The consent process will clearly state what type of information will be collected and that all data provided by participants will be confidential. Participants will be assured that all records will be kept confidential in research files

located in a locked office and entered into a password-protected computer located behind a secure and maintained firewall. Candidates will be sent a copy of the consent form prior to their baseline visit for review. They will be encouraged to ask questions prior to or at the beginning of their baseline visit. Consent will be obtained before data collection procedures at the participant's baseline visit.

Consent forms will be reviewed for completeness and stored in a locked file cabinet in a locked office, away from any material with personal or sensitive study data. Participants will be reassured that they can withdraw from the study at any time.

Comprehension: Misunderstandings will be addressed in real-time through the teach-back method: During the informed consent process potential participants will be asked to summarize the primary study objective and procedures.

Ongoing process: Enrolled participants will have regular communication with study team. The study team will attempt to address any participant concerns over the study that arise in order to strengthen compliance and retention. Ultimately, participants will be reminded that they are volunteering and may withdraw from the study at any time.

4.3.4 Randomization

Participants will be randomly allocated to the intervention or waitlist control arm using blocked randomization (2:1 intervention to control), stratified upon whether the participant has received "AC" chemotherapy (doxorubicin and cyclophosphamide combination therapy).[10] Intervention participants will then be randomized to either aerobic exercise training or resistance strength training, again using blocked randomization stratified on AC treatment history. Randomization will be performed in REDCap with the REDCap Randomization module.

4.3.4 Data Collection

Clinical and self-report data will be collected at 3 total timepoints: baseline, 12 weeks, 24 weeks.

Self-reported data: Participants will be asked to complete baseline questionnaires ascertaining demographic information, health history and current health behaviors. At all timepoints (i.e. baseline, 12-, and 24-Week) participants will be asked to complete self-reported questionnaires on quality of life, physical activity, and fatigue.

Clinic visits: In-person clinic visits will take place at baseline and 24-weeks for all participants. All clinic visits will include anthropometric assessment, MRI, supervised 6MWT and CPET. Participants will complete a supervised 6MWT. Study procedures will occur at the University of Washington Medical Center and the Fred Hutchinson Prevention Center. At intervention completion participants will be asked open-ended questions regarding their experience with the study. The responses will be analyzed for themes to improve future study designs.

Passive Data Collection: Some data will be remotely collected via wrist- and waist-worn actigraphy monitors, worn in the 7 days prior to each clinic visit. Wrist-worn monitors will be worn 24 hours a day including sleep, while waist-worn monitor will be removed for sleep. Wrist-worn devices will also be utilized during all intervention sessions, as a measure of intervention adherence.

Measure	Type of measure	Instrument	Source
Sample Characteristics			
Demographics	Baseline	Questionnaire	Participant
Physical & mental health history	Baseline	Questionnaire	Participant
Intervention Feasibility			
Intervention Feasibility	Primary outcome	Attendance/Retention	Case Report Form
Intervention Acceptability	Secondary outcome	Questionnaire	Participant
Exercise intervention adherence	Other/Exploratory outcome	Actigraphy Monitor	Participant
Exercise intervention adherence	Secondary outcome	RPE	Participant
Intervention session Intensity	Secondary outcome	RPE	Participant
Safety			
Safety	Secondary outcome	Adverse Events	Case Report Form
Cardiorespiratory Fitness			
VO_2 (maximal exercise capacity)	Other/Exploratory outcome	CPET	Case Report Form
Functional Capacity			
6MWD (submaximal capacity)	Other/Exploratory outcome	6MWT	Case Report Form
1 Repetition Maximum (strength)	Exploratory outcome	1-RM	Case Report Form
Physiologic Changes			
Anthropometrics	Other/Exploratory outcome	Physical exam	Case Report Form
Thigh IMF:SM	Other/Exploratory outcome	MRI	Case Report Form
Abdominal fat deposition	Other/Exploratory outcome	MRI	Case Report Form
Patient Reported Outcomes			
Quality of life	Other/Exploratory outcome	SF-12	Participant
Physical activity	Other/Exploratory outcome	PAR/Actigraphy Monitor	Participant
Physical Activity Perceptions	Other/Exploratory Outcome	PA Perceptions & Barriers	Participant
Sedentary behaviors	Other/Exploratory outcome	SBQ	Participant
Perceived well-being	Other/Exploratory outcome	FACT-G Questionnaire	Participant
Insomnia	Other/Exploratory outcome	ISI	Participant
Mood Disturbance	Other/Exploratory outcome	PHQ-4	Participant

Fatigue	Other/Exploratory outcome	FACIT-F	Participant

4.3.5 Schedule of Evaluations

STUDY PROCEDURES	Baseline	Week 12	Week 24
Intervention Arm			
CPET	X		X
MRI	X		X
6MWT	X	X	X
1-RM	X	X	X
Anthropometrics	X	X	X
Questionnaires	X	X	X
Safety (ongoing)	X	X	X
Accelerometry (ongoing)	X	X	X
Control Arm			
CPET	X		X
MRI	X		X
6MWT	X	X	X
1-RM	X	X	X
Anthropometrics	X	X	X
Questionnaires	X	X	X
Safety (ongoing)	X	X	X
Accelerometry (ongoing)	X	X	X

5.0 PARTICIPANT SELECTION

A criterion should be listed as either inclusion or exclusion but not both.

5.1 Inclusion Criteria

1. Age 18 - 75 years, inclusive
2. Female gender
3. Prior diagnosis of invasive breast cancer
4. Completion of chemotherapy or receipt of trastuzumab (Herceptin) therapy within the past 6 – 60 months (0.5 – 5 years)
5. Reduced cardiorespiratory functional capacity, defined as below the median estimated CRF for age/sex-matched controls

5.2 Exclusion Criteria

1. Actively receiving radiation treatment
2. Medical history of heart failure, coronary artery disease or arrhythmia
3. Contraindications to cardiopulmonary exercise testing (CPET)
4. Contraindications to magnetic resonance imaging (MRI) (e.g ferromagnetic cerebral aneurysm clips or other intraorbital/intracranial metal; pacemakers, defibrillators, functioning neurostimulator devices, non-compatible MRI tissue expanders or breast implants, or other implanted non-compatible MRI devices), weight over 550 lbs, or symptomatic claustrophobia
5. Contraindications to exercise, including a history of surgery with sequelae that restrict ability to exercise safely or comfortably
6. Unwilling to complete intervention procedures or outcome measures

5.3 Ethnic/Gender Distribution

TARGETED / PLANNED ENROLLMENT: 30			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	2	0	2
Not Hispanic or Latino	28	0	28
Ethnic Category Total of All Subjects*	30	0	30
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific	0	0	0
Black or African American	6	0	6
White	24	0	24
Racial Categories: Total of All Subjects*	30	0	30

6.0 INTERVENTION PLAN

6.1 Treatment Intervention Arm

Participants in the intervention group will be randomized to receive either AE or RE training. The intervention will comprise of a combination of supervised and unsupervised sessions. Supervised sessions will be led remotely via videoconferencing by a trained fitness instructor, while unsupervised sessions will involve following along with recorded videos. Training protocols will be adapted from the American College of Sports Medicine's (ACSM) guidelines[44,45] and designed to progress in intensity, depending on patient tolerance.

All intervention sessions will include 5 minutes of warm up and 5 minutes of cool down. Warm up and cool down will consist of light aerobics and stretching for both groups. Sessions will occur 3 times a week, with 1 supervised and 2 unsupervised. In the first 3 weeks of resistance training, sessions will occur 2 times per week (1 supervised), to account for increased muscle soreness when starting a resistance training regimen.

Exercise intensity will be measured using the Rating of Perceived Exertion (RPE) scale,[23] which collects respondent's perception of exertion level on a scale from 6-20. Moderate exercise will be considered a 12-13 on this scale, while 14-16 will constitute vigorous exercise.

Participants will rate their perceived exertion after each exercise session, and RPE feedback will be utilized to adjust intensity levels for participants' upcoming sessions.

6.1.1 Aerobic exercise training

Aerobic exercise sessions will entail various standard calisthenics, including such as marching in place, side steps, and jumping jacks. Participants will complete exercises in sets, performing a sequence of exercises for a certain number of seconds each (e.g. 30-60 seconds per exercise) before a rest of 60-240 seconds. The total time of each session will be at least 30 minutes and both the duration and intensity of the sessions will increase during the intervention, as outlined in Appendix D.

Intensity will be varied by adjusting the type of exercise, the number of seconds per exercise and/or the amount of rest time between sets. The intensity will progress, as tolerated, for the first 6 weeks of the intervention, starting at moderate intensity and building to sustained vigorous intensity (see Appendix D). The estimation of intensity will be based off a participant's heart rate (HR) at peak VO_2 from the CPET at baseline. Trained staff will help participants to determine this target HR.

6.1.2 Resistance exercise training

Resistance exercise training will comprise of weight bearing functional tasks (e.g. sit-to-stand) and weighted exercises, with each session targeting upper and lower body large muscle groups. Participants will complete 5 exercises in sets of 1 or 2, performing a sequence of exercises for a certain number of repetitions ("reps") each (e.g. 8-12 reps per exercise) before a short rest. Sets will be separated by a rest of 60-240 seconds.

At baseline testing, study staff will determine participants' one rep maximum for various weighted exercises. The starting weights for the intervention will be based on this measurement.

Intensity can be varied by adjusting the number of reps per set, the number of seconds of rest, or the weight being used.

6.1.3 Combined aerobic and resistance exercise training

The AE+RE intervention will involve a combination aerobic and resistance exercises within session, with approximately half of each session devoted to AE and half devoted to RE (See Appendix E). Aerobic sets will be completed before resistance sets within each session.

6.2 Waitlist Control Arm

The waitlist control group will spend 24 weeks waitlisted for the intervention, during which time they will follow the same schedule of evaluations as the intervention group but will not receive exercise sessions. After completing 24-week assessments, the control group will receive a digital copy of sessions recorded during the intervention group and an outline of sessions for 24 weeks.

7.0 GUIDELINES FOR ADVERSE EVENT REPORTING

7.1 Adverse Event Reporting/Institutional Policy

In accordance with institutional policy, all adverse events which in the opinion of the principal investigator are unexpected and related or possibly related to the research and serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized be reported to the IRB within 10 calendar days of learning of the problem.

Definitions:

Adverse Event - Any untoward medical occurrence in a participant, such as any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the intervention.

Life-threatening Adverse Event – Any adverse event that places the participant, in view of the investigator, at immediate risk of death from the reaction.

Unexpected Adverse Event – An adverse event is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the intervention; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition any predisposing risk factor profile for the adverse event.

Serious Adverse Event (SAE) – Any adverse event occurring that results in any of the following outcomes:

- death
- a life-threatening adverse event (real risk of dying)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly
- requires intervention to prevent permanent impairment or damage

Attribution - The following are definitions for determining whether an adverse event is related to a medical product, treatment or intervention procedure:

- An adverse event is **related or possibly related to the research procedures** if in the opinion of the principal investigator, it was more likely than not caused by the research procedures.

- Adverse events that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related."

- If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

All adverse events will be reported to the University of Washington IRB according to UW guidelines.

7.1.1 Adverse Event Grading

Adverse events will be graded as Mild, Moderate, or Severe using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as a guide: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf See Appendix A, Data and Safety Monitoring Plan.

8.0 DATA AND SAFETY MONITORING

The Principal Investigator will meet with study staff on a monthly basis to review participant's adverse events, verify CTCAE grade, and provide attribution, and to review response data.

This study will employ a Data and Safety Monitoring Plan (DSM; see Appendix A) to outline how participant safety and confidentiality will be managed throughout the study. The PI and co-investigators have clinical licensure (RN or MD) and will review quarterly the following study data provided by the research team:

- Number of participants
- List of adverse event and responses that have occurred in the specified time frame
- Cumulative table of adverse events by type and grade, including deaths as outlined in the protocol-specific DSM
- Premature terminations of the intervention and other safety issues

At each review, the PI and co-I's will determine whether:

- The trial should continue as originally designed
- The trial should be changed
- The trial should be terminated
- Outcome results should be released prior to the reporting of the study results

9.0 DATA MANAGEMENT/CONFIDENTIALITY

This project's varied recruitment strategies involve different types of contact with identifiable health information prior to enrollment. Recruitment streams 2 and 3 outlined in section 4.3.1 will involve potential participants either 1) contacting the study team directly or 2) providing consent for the study

team to make contact.

Recruitment stream 1 will require viewing PHI prior to consent by SCCA breast oncology staff who routinely view this information in their normal workflow. Recruitment stream 4 will involve obtaining PHI prior to consent. The IRB will review and approve all procedures for viewing or obtaining PHI prior to consent. Women who are approached will not be undergoing any serious or sensitive treatments.

All forms of data described in previous sections will be recorded on paper or computerized data forms with no personal identifying information. Candidates for screening will be assigned a 3-digit study ID, and all data collected during screening will be stored with this ID. A 3-digit number will be assigned to each participant, once enrolled. Only the PI and HIPAA-trained study coordinator will have access to the secure OneDrive spreadsheet that links names with subject study identifiers. To ensure confidentiality, no personal identifying information will be coded on the questionnaires or sample data. A separate document will contain contact information but will not contain personal data or protected health information that is collected as part of the study. Study data will be stored in a REDCap database that only the PI and the study coordinator can access. All paper data will be stored in locked file cabinets in a locked office and on password-protected computers located behind a secure firewall.

Data are collected by team members who have completed training in human subject research, HIPAA, research integrity, research data management and confidentiality, and training to criterion on project protocol.

10.0 STATISTICAL CONSIDERATIONS

For objective 1, we will measure the feasibility of our intervention by calculating recruitment rates (% participants enrolled of those approached), enrollment rate (% enrolled of those eligible), lost to follow-up (% who dropped out of those enrolled), intervention discontinuation rate (% of intervention participants who permanently stop the intervention for any reason by Week 24), intervention attendance (% exercise sessions attended), relative dose intensity (% completed sessions), and compliance (based on accelerometry data, self-report of exercise via questionnaires). A benchmark to determine feasibility includes <40% loss to follow-up.

In objective 2, we will start with an analysis of the safety endpoints by calculating the number and percent of adverse events that occurred during the intervention and during the waitlist control period. This analysis will be stratified by the severity of the adverse events, the seriousness of the adverse events, and by the attribution of the adverse events.

The results from above analyses (for Study Aim 1) will be a primary consideration to inform the feasibility and safety of launching a larger scale intervention from the pilot intervention. If both these sets of data provide indications that the study is feasible and safe, then the exploration of additional intervention outcomes will take place. These data will be presented in a manuscript to describe the potential for this intervention. The following analyses will explore additional intervention outcomes to inform the intervention's potential to have an impact on CRF, functional capacity, physiologic changes, and PRO in a larger scale intervention.

Next, the analysis will explore the impact of the intervention on the outcome of CRF in intervention participants versus waitlist control participants using generalized linear models (GLM) comparing baseline to 24-week measurements. This analysis will be repeated for the additional outcomes of functional capacity, i.e., submaximal exercise capacity; physiologic changes, i.e., thigh IMF:SM, abdominal depots of fat (VAT, SQ, RP, and IP fat), and body weight; and patient reported outcomes, i.e., QOL, perceived well-being, and fatigue. These analyses will be performed according to the intent-to-treat principle, where outcomes are analyzed by intervention assigned, regardless of the level of adherence. A secondary per protocol analysis will be conducted, and these results will be reported and interpreted together with the intent-to-treat analysis. This per protocol analysis will include only those participants who (a) completed all clinic visits and who completed at least 85% of the required physical activity. In addition, this secondary analysis will investigate factors related to a lack of intervention adherence, which will include baseline measures of perceived well-being, mood disturbance, perceptions of PA, fatigue, and insomnia.

For objective 3, the analysis will explore the impact of AE vs RE vs combined AE+RE on safety outcomes using generalized linear models (GLM) comparing pre-intervention measurements to post-intervention measurements. Next, this analysis will be repeated for the additional outcomes of CRF, functional capacity, physiologic changes, and patient reported outcomes of QOL, perceived well-being, and fatigue.

In addition, we will explore potential moderators of the intervention, namely baseline BMI and physical activity, and adherence to the intervention for Objectives 2 and 3, and as guidance in designing the subsequent large-scale intervention. First, we will stratify upon BMI to explore whether the intervention showed greater benefit in those with higher BMI. Then we will repeat this for baseline physical activity to explore whether the intervention showed greater benefit in those with lower baseline physical activity. Next, the level of adherence to the intervention will be evaluated by examining the accelerometry data output in conjunction with the self-reported physical activity data. We will also conduct qualitative analyses utilizing data from the elicitation interviews conducted at the end of the intervention. This analysis will summarize data collected from the participants' into themes.

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Appendix A – Data & Safety Monitoring

BRIEF STUDY OVERVIEW

This is a pilot study of a 2-arm SMART-design exercise intervention among breast cancer survivors with reduced cardiorespiratory fitness.

OVERSIGHT RESPONSIBILITIES

Oversight of the trial is provided by Dr. Kerryn Reding, the Principal Investigator (PI), and co-investigators, Rachel Yung, MD and Richard Cheng, MD ("co-investigators" throughout).

MONITORING PROCEDURES

Dr. Reding assures that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PI to review. The PI and co-investigators review study conduct (accrual, drop-outs, protocol deviations) on a monthly basis. The PI reviews adverse events (AE) individually in real-time and with co-investigators in aggregate on a monthly basis. The PI and co-investigators review serious adverse events (SAEs) in real-time. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB according to the applicable regulatory requirements.

COLLECTION AND REPORTING OF SAEs AND AEs

For this study, the following standard AE definitions are used:

Adverse event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or intervention procedure, regardless of whether it is considered related to the medical treatment or intervention procedure.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

Mild: An experience that is transient & requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations. A mild AE typically corresponds to a 1 on the NCI Common Terminology Criteria for Adverse Events (CTCAE).

Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk. A moderate AE corresponds to a 2 on the CTCAE.
Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE. A severe AE corresponds to a 3 on the CTCAE.

The study uses the following AE attribution scale:

Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
Related: The AE is clearly related to the study procedures.

AEs are identified by participant self-report at each study follow up assessments (12-, 24-, 36- and 48-weeks). Participants will be asked about medical or mental health events that have happened since the previous assessment visit. AEs may also be identified during supervised (in-person or remote) exercise sessions, with an event either occurring or being reported during such sessions.

SAEs and specific procedure-associated AEs are reported to the PI and co-investigators within 24 hours. In addition, all AEs are reported according to the University of Washington AE reporting guidelines.

MANAGEMENT OF RISKS TO SUBJECTS

Expected AEs
Expected AEs associated with the exercise intervention include:

- Fatigue
- Muscle Soreness
- Mild Shortness of Breath
- Mild Tachycardia
- Transient increase in blood pressure
- Lightheadedness
- Excessive Sweating
- Muscle strain or sprain

AE Management
Participants experiencing a mild AE (e.g. fatigue or muscle soreness) related to the intervention will have discretion as to whether they want to continue with the intervention exercise regimen. They will be

advised to rest if they want to stop during an intervention session or want to skip a session due to mild AE.

Mild lightheadedness will be treated with slightly more caution than other mild AEs. Participants will be instructed that if during exercise, they experience lightheadedness they should immediately discontinue the exercise. If the lightheadedness persists after discontinuation, they will be instructed to consult a medical professional. If the lightheadedness resolves, the participant can resume normal activities, including the exercise regimen.

If a participant experiences a moderate or severe AE, they will be instructed to cease the exercise regimen for recovery, if necessary, and the PI and co-investigators will evaluate whether re-entry to the exercise regimen is acceptable.

If a participant experiences an SAE, they will be instructed to cease the exercise regimen.

DATA ANALYSIS PLANS

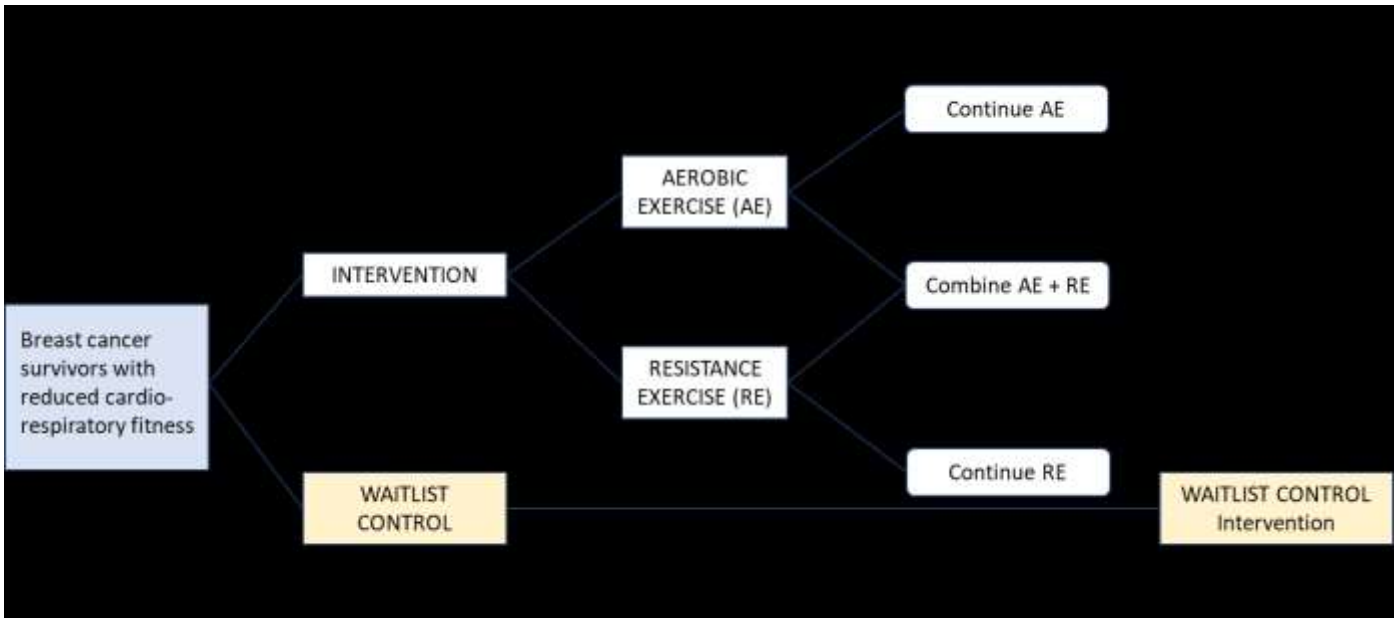
As this is a pilot study, there will be insufficient numbers to conduct a well-powered interim analysis. The study team will examine SAEs and expected AEs in aggregate at the midpoint of the study to examine whether disproportionate SAEs or AEs have occurred in the intervention participants. While there is unlikely to be statistical power in interim analysis, we will conduct bi-variate statistical analysis consisting of chi-square tests to evaluate the proportion of SAEs and AEs in intervention participants versus control participants. The investigators will review this statistical analysis. Discussions of whether sufficient evidence exists for stopping the trial early will involve consideration of whether the AEs are related or unrelated to the study activities.

PLAN FOR DATA MANAGEMENT

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal study team quality assurance process.

Confidentiality throughout the trial is maintained by recording all study data on paper or computerized forms with no personal identifying information. A 3-digit number will be assigned to each subject. Only the PI and the HIPAA-trained study coordinator will have access to the file that links names with subject study identifiers. To ensure confidentiality, no personal identifying information will be coded on the questionnaires or sample data. A separate document will contain contact information but will not contain personal data or protected health information that is collected as part of the study. Study data will be stored in a REDCap database that only the PI and the study coordinator can access. All paper data, including consent forms, will be stored in locked file cabinets in a locked office and on password-protected computers located behind a secure firewall.

Appendix B – STUDY SCHEMA



Appendix C – MRI PROTOCOL

General Overview

This appendix details the abdominal imaging (ABD_LOC and ABD_FAT) and thigh skeletal muscle imaging (3Plane_LOC_Thigh and T1 AX DB Left Thigh_TE36) for participants in the "Investigating Various Adaptive-Training Exercise Programs for Improving Cardiorespiratory Fitness After Breast Cancer Treatment" (ACTIVATE) study. This is a 30-min MR exam. Contact the study team for any clarification on this exam. Different sections of this protocol are as follows:

MRI Protocol– List of Sequences

Body Composition with localizers
ABD LOC
T1 AX ABDOMEN FAT (L2-L4)
3Plane_LOC_thigh
T1 AX DB Left thigh_TE36

***Please place the following information in the Patient Registration Window before the exam begins:**

- Place with the study ID number in the MRN Field.
- Place the acrostic in the Patient Name Field.
- These should be given to you by the Study Coordinator.

Series Name: **ABD_LOC (REF A)**
Series Description: Abdominal Localizer
Notes: Perform multi-plane abdominal localizer (coronal and sagittal). A sagittal plan that appreciates L2-L4 will be used in planning future series.

Series Prescription Details

	Series Rx Notes
Prescribe series from:	Localize the lumbar region
Orientation:	Coronal and Sagittal
Number of Slices	3-5 sagittal slices; 8-10 coronal slices
Breath-holding:	Yes

Image Parameters

Image Parameter	**Value**
Slice Thickness	5mm
Slice Gap	5 mm
TR	260
TE	1.08
Number of Phase Encodings	143
Percent Sampling	75 %
Percent Phase FOV	100%
Pixel Bandwidth	1132
Matrix	192 x 144
Flip Angle	65 degrees

Sample Images

Series Name: **ABD_FAT (REF B)**

Series Description: T1 weighted turbo spin-echo sequence acquired with 3 evenly spaced axial slices with 1st and 3rd centered at L2 and L4.

Notes: To assess visceral fat, a series of images will be acquired to assess visceral fat volume. Open up field of view (FOV) to encompass all of the abdomen.

Series Prescription Details

	Series Rx Notes
Prescribe series from:	ABD_LOC (Ref A)
Orientation:	Axial
Number of Slices	3 evenly spaced axial slices with 1st and 3rd centered at L2 and L4.
Breath-holding:	Yes, breath hold per slice

Sample Series Rx

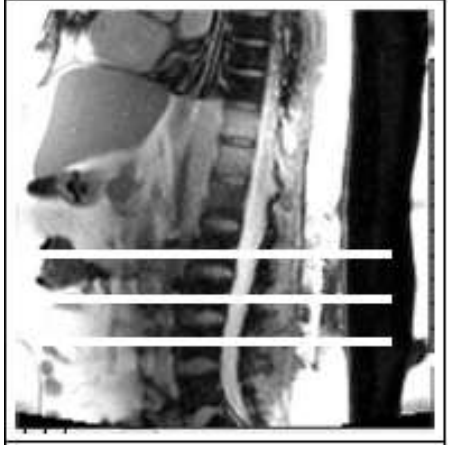
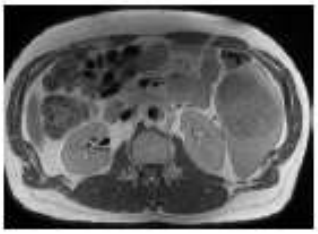
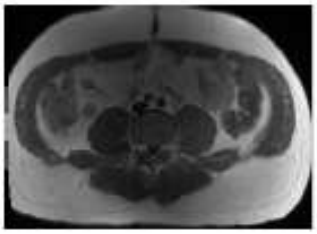


Image Parameters

Image Parameter	Value
FOV	Open to encompass all of the abdomen
Slice Thickness	5mm
Slice Gap	Variable – change distance factor as necessary
TR	800 ms
TE	36 ms
Flip Angle	180 degrees
Matrix	256 * 256
Acceleration factor	2
Bandwidth	305 Hz/Px
Turbo factor	11
Echo trains per slice	13
Gating	ECG triggering

Sample Image(s)





Series Name: **3Plane_LOC_Thigh (REF C)**
Series Description: Thigh Localizer
Notes: Perform multi-plane localizer on thigh with additional body matrix coil.

Series Prescription Details

	Series Rx Notes
Prescribe series from:	3PLANE_Loc_thigh
Orientation:	Coronal, Sagittal, Axial
Number of Slices	3-5 per orientation
Breath-holding:	No

Image Parameters

Image Parameter	**Value**
Slice Thickness	5mm
Slice Gap	5 mm
TR	260
TE	1.08
Number of Phase Encodings	143
Percent Sampling	75 %
Percent Phase FOV	100%
Pixel Bandwidth	1132
Matrix	192 x 144
Flip Angle	65 degrees

Series Name: **T1 AX DB Left Thigh_TE36 (REF D)**

Series Description: T1 weighted turbo spin-echo sequence acquired with 5 evenly spaced axial slices. The position of center slice will be determined by distance measured by study staff.

Notes: A series of images will be acquired to assess muscle and fat composition of left thigh.

Formula for slice location:

* Patient's height in inches x 0.125 = distance from distal femur
* Inches x 25.4 = mm
* Start at distal femur (condyle) and measure up "X" amount of mm to get location for center slice
* Use left leg
* Example: Pt Height = 64.3 inches x 0.125 x 25.4 = 204 mm

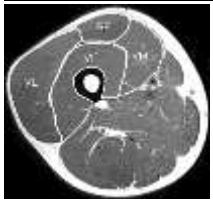
Series Prescription Details

	Series Rx Notes
Prescribe series from:	3PLANE_Loc_thigh
Orientation:	Axial
Number of Slices	5
Breath-holding:	No

Image Parameters

Image Parameter	**Value**
Slice Thickness	5mm
Slice Gap	1 mm
TE	36
FOV	256 x 256 mm^2
Base resolution	384 x 384 pixels
In plane resolution	0.7 x 0.5

Sample Image(s)



MRI Encounter Guide

REF	Series Name	Acq time (~sec)	Series Description / Notes	Series #
A	**ABD_LOC**	9	Sagittal localizer for L2-L4	
B	**ABD_FAT**	3x10	3 evenly spaced axial slices with 1st and 3rd slice centered at L2 and L4	
C	**3Plane_LOC_Thigh**	15	Multi slice localizer of thigh	
D	**T1 AX DB Left Thigh_TE36**	20	Use formula for REF D to plan slice	

The MRI Encounter Form must be completed for each MRI exam. Please use this document as a guide to completing the MRI exam and MRI Encounter Form.

APPENDIX D – Intervention Protocol

Exercise Intervention Overview

Exercise Type	Aerobic	Strength	Combined
Mode	Walking (with guided in-home sessions provided 1 time/week)	Resistance activity (with guided in-home sessions provided 1 time/week)	Both aerobic and resistance activities, starting each session with aerobic activities
Frequency	3 times/week	Level 1: 2 times/week Levels 2 & 3: 3 times per week as tolerated	3 times/week
Time[1]	Level 1: 90 min/week (30 min sessions) Level 2: 120 min/week (40 min sessions) Level 3: 150 min/week (50 min sessions)	Level 1: 60 min/week (30 min sessions) Level 2: 90 min/week (30 min sessions) Level 3: 120 min/week (40 min sessions)	Level 1: 150 min/week (50 min sessions) Level 2: 150 min/week (50 min sessions) Level 3: 180 min/week (60 min sessions)
Intensity[2]	• **Level 1:** 55-60% of HR (at peak VO_2 at baseline) *Target RPE:* 12-13 • **Level 2:** 60-70% of baseline HR *Target RPE:* 13-14 • **Level 3:** 70-85% of baseline HR for duration *Target RPE:* 14-16	• **Level 1:** 50% of 1-rep max per weighted lifts (2 sets of 8-10 reps) *Target RPE:* 12-13 • **Level 2:** 60% of 1-rep max per weighted lift (2 sets of 8-12 reps) *Target RPE:* 13-14 • **Level 3:** 70% of 1-rep max per weighted lift for (2 sets of 10-14 reps) *Target RPE:* 14-16	When the second exercise regimen is added, begin at Level 1 in that regimen while continuing at the same level for the exercise regimen already underway. Sessions will include 20-40 mins of AE and 2 sets of 8-14 reps, with intensities varying based on participant progress

Example aerobic exercises: March in place, jumping jacks, glute kicks, high knees, lateral shuffles, standing oblique crunch, speed skaters, mountain climbers

Example resistance exercises: Weighted lifts and weight bearing functional tasks for large muscle groups; seated knee extensions, standing hip abduction, standing hip extension, triceps extension, and shoulder abduction[3]

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[1]Times do not include 10 min warm-up/cooldown per session (i.e. 20 mins total per wee k in Level 1 resistance training, 30 mins total per week in all other circumstances).

[2]The prescribed progression from Level 1 – 3 includes 3 weeks at Level 1, 3 weeks at Level 2, and the remaining 6 weeks at Level 3. However, participant exertion ratings will be measured after all exercise sessions. The ratings must be at 13 or lower to progress to the next level.

[3]Prior to initiating any activity involving strength training, the following considerations should be made:

- Resolve any acute arm or shoulder problems secondary to breast cancer treatment before exercise training
- Reduce or avoid upper body exercise if exercise causes swelling or changes in arm/shoulder symptoms
- Women with lymphedema should wear a compression garment during exercise
- Be aware of risk for fracture if treated with hormonal therapy, dx of osteoporosis, or bony metastases