PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Women In Steady Exercise Research - Neoadjuvant Exercise Trial

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Version Date:

1.3.2022

Clinicaltrials.gov Registration #:

NCT03280836 "Exercise Program in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy"

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

The primary aim is to determine whether breast cancer patients can be enrolled, randomized, retained, and comply with 6 months of aerobic exercise training; and, the feasibility of acquiring, managing and analyzing the cardiopulmonary fitness, cardiac function, quality of life, and tumor response data.

The secondary aim is to compare changes in hematological parameters (clinical blood biomarkers), cardiopulmonary fitness (VO2max - stress testing), cardiac function (LVEF - echocardiogram), quality of life (surveys), and tumor response (tissue blocks from biopsy and surgical resection, MRI) in exercisers vs. control.

1.2 Primary Study Endpoints

Study completion - feasibility

1.3 Secondary Study Endpoints

n/a

2.0 Background

2.1 Scientific Background and Gaps

Several national and international agencies recommend exercise participation for all persons following a cancer diagnosis (1-3). The current evidence suggests that aerobic exercise training is safe during primary adjuvant therapy and improves cardiopulmonary function and patient related outcomes (1, 4). The vast majority of the studies in the meta-analyses that inform the recommendations and evidence base utilize standard prescription guidelines (50-75% of baseline exercise capacity for 12-15 weeks). Yet, aerobic exercise training prescriptions incorporating high-intensity exercise (85-95% of baseline heart rate peak) elicits superior improvements in exercise capacity compared with standard moderate intensity exercise prescriptions (5-7).

Few studies have tested the efficacy of exercise prescriptions that incorporate high intensity aerobic exercise training in cancer patients, especially those receiving chemotherapy (8-10). Hornsby et al. conducted a randomized phase II trial of 20 women with operable breast cancer initiating anthracycline containing neoadjuvant chemotherapy (11). They utilized a supervised moderate-to-high intensity aerobic exercise training program (60-100% VO2max, 3 days per week) and observed 82% attendance to the supervised sessions and 66% adherence to the exercise prescription. Following assessment of adverse events during stress testing, during aerobic exercise training, clinician reported events (e.g. pain, nausea), and hematological parameters, they found that moderate-to-high intensity aerobic training with one-on-one supervision was safe. This is in line with Rao et al. whom demonstrated feasibility of a bootcamp intervention for 10 women with operable breast cancer initiating anthracycline containing neoadjuvant chemotherapy (12).

2.2 Previous Data

Evidence indicates that aerobic exercise training in breast cancer patients receiving chemotherapy is safe (8, 11, 13-22). It also appears to be efficacious. Hornsby et al demonstrated an increase in cardiopulmonary fitness of 13.3% in the intervention group (11). Cardiopulmonary fitness is highly predictive of overall and cardiovascular specific mortality in women (23-25). Specifically, an increase in cardiopulmonary fitness of approximately 10% has been associated with a 19% reduction in risk for CV mortality (26). This is important as breast cancer patients already present at diagnosis with 31% lower cardiopulmonary fitness levels compared to healthy age-matched women (27). This enhanced risk for

cardiovascular mortality in breast cancer patients is further compounded by cardiotoxic chemotherapy, which causes permanent cardiac damage (28).

It appears that aerobic exercise training is also beneficial for cancer outcomes, as pre-clinical work has shown enhanced tumor response when chemotherapy is combined with aerobic exercise training (29, 30). Clinically, in the same study population as the Hornsby et al study, Jones et al observed changes in circulating endothelial progenitor cells, cytokines, and angiogenic factors (31). Lastly, though underpowered to show significant differences, Rao et al reported smaller tumor sizes and lower Ki-67 scores for the bootcamp intervention group compared to controls (12).

2.3 Study Rationale

We seek to conduct an at home aerobic exercise training intervention in breast cancer patients whom elect to undergo neoadjuvant chemotherapy. We have previously conducted a similar at home aerobic training program for a national cohort of women at risk for breast cancer (32). Utilizing well monitored home based methods for exercise interventions decreases selection bias at enrollment as the intervention is not restricted to women with available resources to attend supervised exercise sessions. Home based exercise programming has similar adherence rates to supervised exercise programming (33). Further, home based exercise programming is more amenable to dissemination than supervised exercise training.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Women with a breast cancer diagnosis (Stage I-IIIC)
- Sedentary (< 75 min/wk of moderate intensity exercise over the past month)
- No previous history of anthracycline based chemotherapy
- Absence of heart disease (clinical diagnosis of coronary artery disease, arrhythmias, congenital heart defects, dilated cardiomyopathy, or valvular heart disease)
- Absence of contraindications for neoadjuvant chemotherapy
- Scheduled to receive neoadjuvant chemotherapy
- Primary attending oncologist approval

3.2 Exclusion Criteria

- Absolute contraindications for exercise stress testing
    - acute myocardial infarction (3-5 days)
    - unstable angina
    - uncontrolled arrhythmias causing symptoms or hemodynamic compromise
    - syncope
    - acute endocarditis
    - acute myocarditis or pericarditis
    - uncontrolled heart failure
    - acute pulmonary embolus or pulmonary infarction
    - thrombosis of lower extremities
    - suspected dissecting aneurysm
    - uncontrolled asthma
    - pulmonary edema
    - room air desaturation at rest ≤85%
    - respiratory failure
    - acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise
    - mental impairment leading to inability to cooperate
    - decisional impairment
- Non-English speaking
- Women only diagnosed with ductal carcinoma in situ

- Women diagnosed with stage 4 metastatic breast cancer
- Pregnant women
- Men
- Children

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Subject consent withdrawal
Development of contraindication to exercise testing or training
Subject is imprisoned, committed to a mental hospital, hospitalized for long term care, admitted to a drug/alcohol residential program, a residential living facility or alike.

3.3.2 Follow-up for withdrawn subjects

No follow up for withdrawn subjects

4.0 Recruitment Methods

4.1 Identification of subjects

PSCI

Study staff will conduct an initial eligibility screening based on chart review to determine if the patient is eligible based on the following inclusion criteria: female, not pregnant, breast cancer diagnosis (Stage I-IIIC), no previous history of anthracycline use, absence of heart disease. If the patient is eligible the study staff will contact the treating oncologist for permission to approach the patient.

Andrews Patel

Similar to above, a research nurse will weekly screen whether there are new breast cancer patients scheduled to receive chemotherapy. Following identification of these patients, the research nurse will obtain physicians approval to approach patient.

4.2 Recruitment process

PSCI

Patients meeting initial eligibility criteria for this study will be contacted by study staff over the phone or in-person. Study staff will confirm the patient does not present with the following exclusion criteria: acute myocardial infarction, unstable angina, uncontrolled arrhythmias causing symptoms or hemodynamic compromise, syncope, acute endocarditis, acute myocarditis or pericarditis, uncontrolled heart failure, acute pulmonary embolus or pulmonary infarction, thrombosis of lower extremities, suspected dissecting aneurysm, uncontrolled asthma, pulmonary edema, room air desaturation at rest ≤85%, respiratory failure, acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise, mental impairment leading to inability to cooperate. Study staff will then discuss the study in detail to make the patient aware of the procedures, intervention, and time commitment involved with the study.

Andrews Patel

If the medical oncologist gives clearance, the research nurse will approach the patient either by phone or in-person for presentation of the study. During this phone call / meeting, the nurse will briefly explain the trial, and will ask for permission to give contact details of the patient, and some clinical info to Penn State study staff. If the patient gives permission, study staff will contact the patient to provide more information about the study and confirm the additional eligibility questions (see phone script).

4.3 Recruitment materials

4.4 Eligibility/screening of subjects
See above.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

PSCI and Andrews Patel: If the patient remains interested in the study after screening and recruitment, study staff will schedule a joint consent session and baseline visit at the exercise testing facility. This visit will be scheduled before or following another clinical visit in order to minimize visits to the institution. During the consent session we will answer any remaining questions and we will obtain written informed consent prior to any study activities.

5.1.1.2 Coercion or Undue Influence during Consent

While exercise is recommended during cancer treatment, women will be reminded that self-directed walking is also an available alternative for them.

5.1.2 Waiver or alteration of the informed consent requirement

Requested for screening/recruitment purposes only

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written informed consent will be obtained prior to initiating any study related actives with the patient.

5.2.2 Waiver of Documentation of Consent

If a subject is interested in enrolling in the clinical trial (i.e. expresses interest to the clinician for the researchers to call her), this will be considered implied consent. Researchers will conduct the telephone script and schedule to meet with the subject to obtain formal written consent.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Study staff are not fluent in languages other than English.

5.3.2 Cognitively Impaired Adults

n/a

5.3.2.1 Capability of Providing Consent

This will be determined by the oncologist.

5.3.2.2 Adults Unable To Consent

A contraindication to exercise stress testing, and thus an ineligibility criteria is mental impairment leading to inability to cooperate.

5.3.2.3 Assent of Adults Unable to Consent

n/a

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

n/a

5.3.3.2 Assent of subjects who are not yet adults

n/a

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

We will identify eligible patients through electronic medical records prior to their consent in the study (pre-screen eligibility criteria). This information will be collected/retained on patients whom consent to be part of the study. No information from this screen will be collected/retained on patients whom do not consent to be part of the study.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

We will be conducting exercise testing and counseling (for those randomized to the intervention group) prior to starting chemotherapy. The timeline between recommendation for chemotherapy and initiation of chemotherapy is often short. Therefore, it is imperative we initiate recruitment for the study as soon as possible and thus schedule research visits on the same days as the patient comes to the Cancer Institute for testing related to their clinical treatment.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Pre-screening individuals through electronic medical records allows for the timing of physician approval and approach of the patient. This study flow is being utilized to minimize patient burden for excess visits to the Cancer Institute for the research study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Phase II randomized controlled trial, computer generated randomization. Investigators were blinded to randomization generation.

7.2 Study Procedures

7.2.1 Clinical covariates:

Detailed clinical covariates will be obtained (following consent at the participant's first hematology/oncology appointment) from questionnaires and medical record review including demographics (age, gender, race), cardiovascular history and risk factors (hypertension, arrhythmia, hyperlipidemia, tobacco use, family history of cardiac disease), clinical variables (blood pressure, weight), treatment regimen (ACT, TAC, CAF), and medication use.

7.2.2 Blood sampling:

Blood sampling for research purposes will occur in conjunction with clinical blood draws or prior to chemotherapy infusion to limit inconvenience to the research subjects. Approximately 16 ml of blood will be obtained during a clinical blood draw prior to initiation of cancer therapy and 16 ml following completion of anthracycline dosing (HER2- patients receiving ACT) or at cycle 3 (HER2+ patients receiving TCH+pertuzumab), as well as 16 ml following completion of

chemotherapy (two 8ml tubes – (1) EDTA and (1) Serum). Plasma, serum, and buffy coat (if applicable) will be aliquotted and stored. All spinning, aliquotting, and storage will occur in the Clinical Research Biospecimen Core Lab (C6529) or in the PI's lab. Blood sampling will be done in the usual fashion with standard phlebotomy precautions. EDTA plasma will be used to assess metabolomics and cytokines.. One ml of serum will be used for a chemokine multiplex panel. If consented to by the participant, 1ml off serum or plasma will be used to evaluate level of cell-free DNA (tumor DNA). Buffy coat will be used to assess epigenetic changes in immune cells (white blood cells) or somatic DNA.

7.2.3 Transthoracic echocardiogram:

Resting echocardiograms with conventional measures of systolic and diastolic function, as well as measures of strain and strain rate will be obtained at baseline and following chemotherapy. Conventional resting echocardiograms are obtained clinically before chemotherapy (as well as during and after neoadjuvant chemotherapy for HER2+ patients). Resting echocardiograms are not obtained clinically following chemotherapy for HER2- patients; therefore this measurement is additional for research. There will be no additional costs to the patient for any of these echocardiograms. Echocardiograms that are performed as part of clinical care will be read in the conventional manner and reported in the subject's medical record as per routine care. For patients receiving a follow up research echocardiogram we will call the patient to share clinically relevant results.

7.2.4 Maximal oxygen consumption (VO2) test:

All subjects will undergo a treadmill exercise test to estimate maximal oxygen consumption (VO_2max) as an index of cardiopulmonary fitness. Prior to beginning the test, electrodes will be positioned on the subject's torso in order to acquire a 12-lead ECG and heart rate. Resting ECG, heart rate, and BP will be obtained prior to beginning the test, during each stage of the test, and for 5 minutes after the test is stopped (recovery period). Subjects will begin an incremental treadmill protocol with a change in workload (speed and/or grade) every 3 minutes (Modified Bruce Protocol). At each stage of the test, subjects will indicate their Rating of Perceived Exertion (RPE) using a Borg category-ratio scale. The workload will be increased until subjects reach 80% of their age-predicted HRmax. During this test, VO_2 will be measured by open circuit spirometry. Subjects will wear a nose clip and breathe through a mouthpiece to collect expired air. Ventilation, CO_2 production, and the respiratory exchange ratio (RER; expired VCO_2/VO_2 consumed) will be continuously measured. When the test ends, the treadmill grade will be decreased to 0% while the subject continues to walk slowly for several minutes. The subject will then be seated in a chair for the remaining recovery period. ECG, heart rate, and BP will continue to be monitored until heart rate decreases to within 10 beats/min of their resting heart rate. VO_2 measurements and HR response to the protocol will be used to predict VO_{2max}. If, during the baseline exercise test we have to terminate the test for an absolute indication (other than participant's request to stop/volitional fatigue) we will recommend to the participant that they contact a medical provider (primary care physician/cardiologist) to follow up on our observations.

7.2.5 Aerobic exercise training intervention:

All participants randomized to the intervention group will be asked to keep an exercise log with the date, time, average heart rate obtained from a heart rate monitor, duration of workout and stretching, and any comments regarding the workout. Participants will be instructed to bring workout logs to infusion sessions for review. Participants will also wear a Polar Heart Rate monitor (US model RS400, Polar Electro Inc., Lake Success, NY) during exercise to monitor exercise intensity. The heart rate monitors will be brought back to the Medical Center at infusion sessions in order for the staff to objectively monitor exercise adherence. A member of the research team will collect data at these infusion sessions (exercise logs and watch). A

second watch, stripped of any participant data, is given back to participants to continue exercise training.

The aerobic exercise intervention will work toward the target of 75 minutes of aerobic exercise per week at 60%-85% of baseline VO2max. Walking has been chosen because it is the preferred mode of exercise training for breast cancer patients. (34)

In Weeks 1-4 (Introductory Phase) of the program, the frequency, duration, and intensity of aerobic exercise will be progressively increased from an initial prescription of 3 session/wk for ~20 mins/session at ~60% of VO2max to ~25 mins/session at ~65% of VO2max at the end of week 4. The goal of these sessions will be to introduce aerobic exercise, including warm-up as well as walking pace and proper form.

In Weeks 5 to 11 (Intermediate Phase), the goal will be to introduce higher intensity aerobic exercise. Specifically, aerobic exercise intensity will range between ~60%-70% VO2max for two sessions per week; in the remaining session, aerobic exercise intensity will be set at ventilatory threshold (~75% VO2max).

In Weeks 12 to 24 (Maintenance Phase) participants will be asked to perform 3 aerobic exercise sessions per week at ~60%-75% VO2max with sessions ≥25 minutes in duration with the intensity of the once per week harder sessions ≥80% VO2max.

An exercise physiologist will contact the participants weekly via phone or in person during their infusion visit to troubleshoot and provide support.

7.2.6 Control group activities:

Participants randomized into the control group were asked to maintain their usual level of physical activity and to not engage in any new exercise program during study participation. Participants in the control group will be contact at each infusion session and asked about their experience and well-being during treatment (i.e. attention control). Participants in the control group will have DVDs and an exercise binder shipped to their house following: completion of all study visits (including their exercise safety education session), and clearance from surgical oncology.

7.2.7 Quality of life surveys:

Physical Activity Questionnaire, Work Productivity and Activity Impairment Questionnaire (WPAI), EuroQol 5D (EQ-5D), Medical Outcomes Study 36-Item Short Form (SF-36), Fatigue Symptom Inventory (FSI), short form, and the Adverse Effects survey. These will be administered during the first chemotherapy infusion session, a midpoint chemotherapy session (defined above for blood draws), and at the last neoadjuvant chemotherapy session. The Injury History Questionnaire is administered following chemotherapy.

7.2.8 Exercise education session:

Participants randomized to the intervention will be oriented to the exercise intervention in person at their baseline cardiopulmonary exercise test before they receive intervention materials. Orientation will include instruction regarding the proper use of heart rate monitors, as well as how to warm-up, cool-down, stretch, proper footwear for injury prevention, aerobic exercise equipment safety, and completing the exercise logs. Those randomized into the exercise group will then be given three DVDs and their exercise intervention binder. The exercise physiologist will then provide ongoing support and monitoring of adherence in person at infusion sessions or via phone. The control group will also receive the same exercise education session as above following final exercise testing. Additionally, following surgical

resection and completion of all study visits DVDs and exercise binder will be given or shipped to the participant.

7.2.9 Breast tissue from biopsies/surgery
H&E stained slides from diagnostic clinical pathology assessment will be viewed by a clinical pathology fellow and assessed for tumor infiltrating lymphocytes (TILs).

7.3 Duration of Participation

Estimated time to enroll all subjects = 12 months
Length of a participant's participation = 8 months

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Enrolled: 20

8.2 Sample size determination

N=10 intervention
N=10 control

Our intervention protocol is adapted from Hornsby et al. They report a final VO2 of 1.6 ± 0.35 L/min in the intervention group and 1.2 ± 0.23 L/min in the control group. Thus, we are powered at 80% to see the same difference in VO2 with 10 people per group assuming unequal variances. We have powered off of VO2 as it is our physiological measure of intervention success per physiological adaptation.

8.3 Statistical methods

Fisher's exact tests and $\chi 2$-tests will be used to examine between group differences in the overall proportion of patients experiencing treatment-related and training-related adverse events. A mixed-model repeated measures analysis of variance will be used to compare between group differences over time for outcome variables related to: cardiopulmonary fitness (VO2max - stress testing), cardiac function (LVEF - echocardiogram), and tumor response (MRI). All efficacy outcomes will be assessed under the intention to treat principle. A two-sided significance level of 0.05 will be used for all statistical tests.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Participant's medical records will be monitored at every infusion appointment.

10.2 Data that are reviewed

Laboratory reports and clinician progress notes.

10.3 Method of collection of safety information

Case report form to document monitoring and results of monitoring.

10.4 Frequency of data collection

Every cycle of chemotherapy.

10.5 Individuals reviewing the data

Oncology fellow, and Kathleen Sturgeon.

10.6 Frequency of review of cumulative data

We will review following the mid point of enrollment (10 women randomized), and following the completion of half of the cohort (10 women finished the study).

10.7 Statistical tests

Fisher's exact tests and χ2-tests will be used to examine between group differences in the overall proportion of patients experiencing treatment-related and training-related adverse events.

10.8 Suspension of research

n/a

11.0 Risks

The risk of maximal cardiopulmonary exercise testing is approximately 1 nonfatal event in 10,000 maximal treadmill tests and only 1 fatal cardiac complication in over 70,000 maximal exercise tests. Major complications of exercise testing include death, fatigue, myocardial infarction, arrhythmia, hemodynamic instability, and orthopedic (bone, muscle, tendon, joint) injury. Skin irritation may occur at the sites where electrodes were placed.

The risk of an exercise training induced CV event is 2 nonfatal CV events in 375,000 subject hrs of exercise, or about 1 event per 1.7 million walk/jogging miles, based on a large Dallas, TX physical activity center study. Cardiovascular risks associated with exercise training are: abnormal heart rate or rhythm, heart attack, stroke, or even death.

Other risks of exercise training include: muscle pain, muscle strains/sprains, joint pains (such as hip, knee, ankle or foot pain), fatigue, risk of fall resulting in trauma/fracture.

There are no serious risks associated with transthoracic echocardiography. It is possible that subjects may experience mild, temporary discomfort from the ultrasound probe being pressed against the chest or from lying in the recumbent position for the duration of additional imaging.

There are no medical risks associated with filling out surveys, however a woman may become uncomfortable providing personal information. Any questions that make them uncomfortable can be skipped.

No additional blood draws will be done outside of standard clinical care.

There is a risk of loss of confidentiality if your medical information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Participants randomized to the intervention whom comply with study procedures will increase their cardiopulmonary fitness and decrease their risk for cardiovascular disease.

12.2 Potential Benefits to Others

The information obtained from this research study may benefit future breast cancer patients by demonstrating safety and efficacy of an at home aerobic exercise intervention. Such an intervention may improve cardiopulmonary fitness, cardiac function, and tumor response to chemotherapy. Information obtained in this study may help us increase the effectiveness of neoadjuvant chemotherapy while also decreasing cardiotoxic side effects.

13.0 Sharing Results with Subjects

We will tell participants in the intervention arm if they increased their fitness level following completion of exercise testing. We will also tell HER2(-) participants clinically relevant results of their research echocardiogram.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subjects in the control arm will receive DVDs and the exercise binder following the completion of final testing. Subjects in the intervention arm will receive DVDs and intervention materials (exercise binder and exercise logs) prior to starting chemotherapy. No other compensation will be given for time or travel.

15.0 Economic Burden to Subjects

15.1 Costs

None

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Recruitment and testing will be conducted at the Penn State Hershey Medical Center, the University of Pennsylvania, and Andrews & Patel Associates. Patients recruited at Andrews & Patel will have exercise testing conducted at the HCAR building and echocardiograms conducted within the Penn State Health system (same as PSCI patients). Patients recruited at the University of Pennsylvania will have tests conducted at the below locations:

	Baseline Visit (before starting chemotherapy)				During chemotherapy			Final Visit (after completion of chemotherapy, before surgery)				
RESEARCH ACTIVITY	**Exercise Test**	**Education Session**	**Surveys**	**Blood Draw**	**Exercise Intervention** 60-75+ min/wk	**Phone Call** weekly	**Phone Call** Each chemo cycle	**Blood Draw**	**Education Session**	**Exercise Test**	**Echo[3]**	**Surveys**
Location	*EMU[1]*	*EMU*	*EMU or Home*	*PCAM[2] (in infusion)*	*Home*	*Home*	*Home*	*PCAM (in infusion)*	*EMU*	*EMU*	*EMU or PCAM[2]*	*EMU or Home*
Length of Time	45 min	1 hour	30 min	2 min	Up to 75 min/week	10 min/week	5 minutes each	2 min	1 hour	45 min	45 min	30 min
GROUP												
Control	X		X	X			X	X	X	X	X	X
Intervention	X	X	X	X	X	X		X		X	X	X

[1] EMU – Exercise Medicine Unit at Penn Presbyterian Hospital (51 N 39th St, Philadelphia, PA)
[2] PCAM – Perelman Center for Advance Medicine at the Hospital of the University of Pennsylvania (3400 Civic Center Blvd, Philadelphia, PA)
[3] Research Echocardiogram (echo) will be done for patients whose cancer is not treated with Herceptin (trastuzumab).

Dr. Kathryn Schmitz is the Director of the Exercise Medicine Unit at the University of Pennsylvania where the testing will be conducted. Further, Upenn PI Dr. Bonnie Ky has several ongoing studies that utilize the echocardiogram services in the Human Phenotyping Core, which is housed in the Exercise Medicine Unit.

16.2 Feasibility of recruiting the required number of subjects

We aim to recruit 20 eligible patients undergoing neoadjuvant chemotherapy regimens.

Penn State (combination of PSCI and Andrews Patel) n=10
University of Pennsylvania n=10 We have added these sites to increase our recruitment pool and meet our recruitment goal.

16.3 PI Time devoted to conducting the research

The PI has assembled a research team composed of clinicians and researchers whom will carry out and oversee the study. In particular, study co-PI, Dr. Sturgeon, has 10% dedicated effort to the study and a pilot grant from NRG Oncology to support the sub-awards to sites.

16.4 Availability of medical or psychological resources

All necessary equipment to take part in this study is provided. Further, research staff will be interacting with participants at their infusion visits to trouble shoot any issues associated with the study.

16.5 Process for informing Study Team

All study team members have been involved in the development of the study and have approved study protocols. Measurement staff has been trained on how to do the measurements in a standardized way. Dr. Sturgeon has worked with the lead at the EMU, Margaret Evangelisti MS, on the WISER Survivor study at Upenn as a post-doc and Dr. Sturgeon has developed the clinical protocols in use for exercise testing at the EMU. Thus, exercise specialists have been trained on how to conduct the exercise testing. To guarantee fidelity of the intervention within and between sites Dr. Sturgeon will be the only exercise physiologist that conducts the intervention. Further, we have worked with the REDCap data management team for fidelity on data collection and management.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Approval letters from the Upenn IRB and CTSRMC and Andrews & Patel Associates are included with this submission.

17.2 Internal PSU Committee Approvals

Check all that apply:

☒ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☒ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans

Dr. Sturgeon will email or speak with the site coordinators (Andrews & Patel and Upenn) at regular intervals when a subject is enrolled in order to coordinate study procedures. Dr. Sturgeon will attend in person or via phone Dr. Ky's lab meetings at Upenn once per month to troubleshoot and discuss any study related topics with Dr. Ky and her research coordinators. This monthly interaction will ensure that protocol modifications, consent documents, and MOPs are up to date. Further, this tracking will be supplemented by the REDCap eRegulatory Binder which will be audited quarterly. Following completion of recruitment and of the last patient through the study, Dr. Sturgeon and Dr. Schmitz will attend Dr.

Ky's lab meetings quarterly (via phone) to facilitate analysis of results, lesson's learned, and study close out.

18.2 Data Submission and Security Plan

Data and specimen transfer agreements are pending.

Dr. Sturgeon is working with the PHS Data Management unit to extend the REDCap project and appropriate data restrictions to Upenn coordinators. Upenn will have their access restricted to participants enrolled from their site. Dr. Sturgeon will access PHI from all sites in REDCap in order to conduct the intervention. In addition, Dr. Sturgeon will receive data from Upenn and Andrews & Patel sites into separate KiteDrive workspaces. Data elements abstracted from patient medical records will be inputted into REDCap. Further, surveys are delivered directly to the participant via REDCap and therefore will be updated in real time. These plans were developed with Upenn and conform to all local information security policies.

Blood samples will be stored at Upenn and Andrews & Patel.
They will only be shipped to Penn State after material transfer agreements are in place.

18.3 Subject Enrollment

Upenn – n=10
PSU – n=10 (between PSCI and Andrews Patel)

Eligible patients whom have consented to the study will be enrolled onto the study and the baseline exercise test will be conducted. The exercise test is conducted at HCAR at the HMC campus for PSCI and Andrews & Patel patients, and conducted at the Exercise Medicine Unit at Upenn for Upenn patients.

Following the baseline exercise test, the measurement technician whom conducted the exercise test will open the sealed envelope (labelled with the patient study ID#) that resides in each study binder. Each envelop contains the intervention group assignment for the respective study ID#. Thus, patients will be randomized following the exercise test. The randomization sequence was generated, assigned to patient ID#s, and envelops created, at study start up.

18.4 Reporting of Adverse Events and New Information

The PIs (Drs. Ky, Schmitz, and Sturgeon) will be notified of any adverse events as the study team becomes aware of them and events will be reported to the IRB, according to relevant institutional policies (19.1 below). Adverse events to be monitored (in both groups) include musculoskeletal injuries and cardiopulmonary emergencies. Events will be graded according to the CTCAE v4.0. The PIs will determine if the adverse event is definitely, probably, possibly, or not related to the study intervention. Adverse event monitoring will start at the baseline visit and will continue until subject completes all protocol related activities or is withdrawn. Dr. Ky will report each serious adverse event to Dr. Sturgeon within 24 business hours of learning of the occurrence. In the event that Dr. Ky does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), Dr. Ky is to report the event within 24 business hours after learning of it and document the time of her first awareness of the adverse event.

18.5 Audit and Monitoring Plans

Dr. Sturgeon will audit the Upenn site through the use of the REDCap eRegulatory Binder (Andrews & Patel will not use the eRegulatory Binder as they are under the PSU IRB). Dr. Sturgeon is working with the PHS Data Management Unit to implement this REDCap based organization of regulatory documents to track and review regulatory items. As Dr. Sturgeon is also the study interventionist she will monitor the study continuously due to hands on interaction with Upenn and Andrews & Patel coordinators. Additionally, activities related specifically to screening, recruitment, and data management are

standardized through the use of manuals of operations (MOPs). At both sites, following the successful enrollment of the first patient a monitoring visit will be conducted by Dr. Sturgeon to make sure data elements are captured correctly and protocols are followed. The monitoring and audit MOPs will be further developed because of this multi-site pilot, for use in a multi-site national trial.

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored

De-identified plasma, serum, and buffy coat in aliquoted tubes (~500ul/tube) will be stored and labeled with study name, study ID number and visit time point.

21.2 Location of storage

Samples will be stored in the Sturgeon Lab in a -80 degree freezer on the third floor of the Cancer Institute.

21.3 Duration of storage

Sample will be banked indefinitely to facilitate plans for additional analysis as informed by the results of the WISER-NET study.

21.4 Access to data and/or specimens

The samples will be immediately available to Dr. Sturgeon and research team at the appropriate time. However they will stored in a freezer located behind a password-protected entry. All samples will be labeled with the study name, the participant ID, study visit and date of blood draw.

21.5 Procedures to release data or specimens

Dr. Sturgeon will approve specimen release. The release procedures will be dictated by the Material Transfer Agreement (MTA).

21.6 Process for returning results

Results will be returned to Dr. Sturgeon according to the MTA.

22.0 References

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