Title: The effect of combined aerobic and muscle strengthening exercises on structural and functional cardiovascular adaptations in endometrial cancer survivors.

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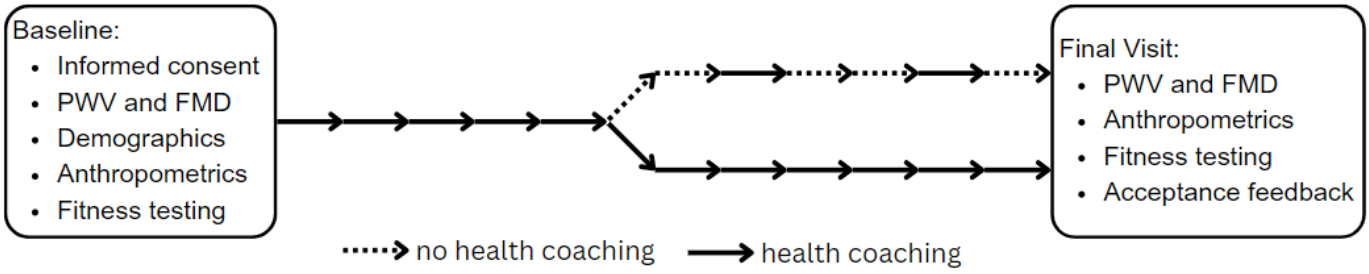
STUDY SCHEMA

Five weeks of weekly health coaching followed by either:

- Tapered health coaching (sessions only during weeks 8 and 11)

OR

- Continued weekly health coaching (sessions continue weekly through week 12)



Twelve weeks of home-based exercise including:

- two days/week of full-body muscle strengthening exercises
- Aerobic activity aiming to achieve 150 mins/week

Revision History

Version 1, Version Date 1/13/2025

Protocol Version	Date	Change Initiated (Initials)	Brief description of protocol modification/actions requested, if any
Version 1.0	06/05/2024	JG	Primary version
Version 1.1	07/03/2024	JG	Revising protocol for additional health history information, participant materials description
Version 1.2	09/27/2024	AB	Revising protocol to expand inclusion criteria, study population description
Version 1.3	10/11/2024	AB	Adding short performance physical battery measures
Version 1.4	11/15/2024	AB	Revising protocol to include recruiting participants from the Iowa Cancer Registry
Version 1.5	1/13/2025	JG	Removing Andrea Babcock from the protocol, has left team
Version 1.6	2/10/2025	JG	Clarifying inclusion criteria regarding treatment resistant hypertension and adding triglycerides as one of our blood biomarkers
Version 1.7	4/15/2025	JG	Updating sample size to n=33 to account for 10% dropout for analytic sample size of 30

Contents

List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
ASCVD	Atherosclerotic cardiovascular disease
CFR	Code of Federal Regulations
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	U.S. Food & Drug Administration
FFT	Functional Fitness Test
FMD	Flow mediated dilation
HCCC	Holden Comprehensive Cancer Center
ICH	International Conference on Harmonization
IIT	Investigator Initiated Trial
IME	Important Medical Event
IRB	Institutional Review Board
OMB	Office of Management and Budget
OPEN	Observing Protein and Energy Nutrition
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
PWV	Pulse wave velocity
RPE	Rate of Perceived Exertion
SAE	Serious Adverse Event
SPPB	Short performance physical battery
ICR	Iowa Cancer Registry

1. Abstract

Background: Endometrial cancer survivors (ECS) are more likely to die from cardiovascular disease (CVD) than any other cause, and exercise is an established intervention to lower the burden of CVD. The development of endometrial cancer is associated with obesity, physical inactivity and cardiometabolic dysfunction which will often persist without significant intervention. We have an established exercise protocol for improving strength and aerobic fitness in ECS but the mechanism by which exercise can mitigate secondary and latent effects of cancer treatment, which if controlled could lower longer-term risk of CVD or CVD-associated mortality, is unknown. Understanding the mechanistic adaption for exercise as a cancer control strategy is essential as ECS have a disproportionately high burden of CVD risk factors, metabolic dysfunction, obesity, and effects of treatment.

In our first year of ACS IRG funding, we successfully completed our two aims which included a qualitative analysis of inactive endometrial cancer patients (on treatment) to understand their perceptions, knowledge, and preferences for exercise. We found that this group overwhelmingly wanted tailored, home-based exercise programs. In our second aim, we successfully completed our aerobic, muscle strengthening exercise protocol in ten ECS who had large improvements in strength and aerobic fitness, with high exercise adherence and satisfaction with the intervention.

Objective/Hypothesis: Our primary objective is to measure changes in biomarkers of vascular structure and function following our combined aerobic and muscle strengthening exercise in endometrial cancer survivors. We hypothesize that there will be clinically meaningful improvements in structural and functional vascular biomarkers, and improved composite risk scores.

Specific Aims: Our two aims are to (1) Quantify the changes in vascular structure (pulse wave velocity) and function (flow mediated dilation) following a distance-based exercise program; and (2) Determine the magnitude of changes in ASCVD risk profiles following a distance-based exercise program.

Study Design: A single arm, pre-post experimental study.

Cancer Relevance: Endometrial cancer is an increasingly common diagnosis, with latent cardiometabolic threats to health that persist for years following treatment. Exercise in cancer survivors has the potential to reduce cancer burden via cardiovascular fitness, quality of life, strength, longevity, and independence. This study focuses on how exercise can improve vessel structure and function in endometrial cancer survivors, a population that has a high burden of CVD risk factors prior to treatment, and cancer treatment can make these risk factors worse. By understanding how exercise as a supportive therapy to improve the health of endometrial cancer survivors, we can reduce the longer-lasting effects of cancer in this population.

2. Background / Rationale

Exercise guidelines for cancer survivors include both aerobic and muscle strengthening exercise components to maximize health, reduce the risks of chronic illness including cardiovascular disease (CVD), and to combat common patient reported symptoms post-treatment including anxiety, depression, and cancer-related fatigue[1]. Despite these numerous benefits, less than 10% of endometrial cancer survivors meet these guidelines[2]. Endometrial cancer survivors have a high burden of cardiometabolic symptoms including metabolic syndrome, diabetes, obesity, and cardiovascular dysfunction which threaten both quality and quantity of life[2,7]. Cancer treatments also directly impact physiologic function. In a population-based study of 2648 endometrial cancer survivors, those who received surgery and radiation, surgery and chemotherapy, or a combination of all three treatments had 24% (HR 1.24 CI 1.00-1.53), 242% (HR 3.42 CI 2.24-5.21), and 92% (HR 1.92 CI 1.31-2.83) excess risk (respectively) for developing arterial disease within 1-5 years of cancer diagnosis[7]. For all risk factors, receipt of chemotherapy is the most significant risk factor for disease of the arteries, diseases of veins/lymphatics, and heart disease within five years of diagnosis[7]. The highest risks in endometrial cancer survivors were observed within the first 1-5 following treatment, but elevated risks persisted for 5-10 years following treatment[7]. In fact, the leading cause of death in endometrial cancer survivors is CVD over all causes. This burden of CVD dysfunction and risk factors is a *growing threat to cancer control* as exercise is one of the few well-established interventions for lowering risk of arterial dysfunction, CVD, and premature death.

First year success: Our theory-based exercise approach produced behavior change and fitness improvements. In our first year of ACS IRG funding, we demonstrated that our remote, home-based exercise format, informed by the Social Cognitive Theory (SCT), was successful on targeting on key theoretical constructs of environment, behavioral, and cognitive factors that facilitate exercise[8]. Our first year of ACS IRG funding yielded clinically significant improvements in lower body (effect size ES=0.71) and upper body (ES=1.21) strength as well as aerobic endurance (ES=0.56) in endometrial cancer survivors. Our ten participants were highly adherent to the aerobic (89% compliant) and the muscle strengthening (75% compliant) exercise protocols. In this proof-of-concept design, we efficiently recruited ten endometrial cancer survivors who all (*n*=10) were retained and completed follow up testing, they also reported high (100%) satisfaction with intervention components. *We will build on our approach to include cardiovascular measures as our primary outcome while also measuring exercise behavior, and changes in cardiovascular risk profiles.*

Cardiovascular and arterial dysfunction are impaired by cancer treatment, and both predict CVD and early mortality. In endometrial cancer survivors, cardiometabolic changes and vascular dysfunction often predate their cancer diagnosis[7], but these conditions are exacerbated by treatment and worsen in the early survivorship period within five years of diagnosis[7]. While vascular adaptions to exercise have been established in other populations, to date no study has examined the vascular and cardiometabolic response to exercise in endometrial cancer survivors, which has been shown to be impaired following cancer treatment[7]. To examine vascular function, pulse wave velocity (PWV) will be used as a measure of vessel structure and stiffness; additionally, we will measure brachial artery flow mediated dilation (FMD) as a measure of endothelial function. We will generate atherosclerotic CVD (ASCVD) risk scores, a composite measure of traditional risk factors estimating 10-year risk of CVD-death[3]. The ASCVD risk score is sufficiently sensitivity to change (Duttagupta et al. 2022).

OBJECTIVE. We aim to quantify changes in vascular biomarkers of CVD risk including FMD, PWV and ACSVD risk scores in endometrial cancer survivors following a home-based exercise program. To our knowledge, this would be the first investigation of these clinical biomarkers in endometrial cancer survivors, a population with high cardiometabolic risk factors and high burden of CVD. *Our first year of ACS-IRG funding revealed meaningful functional strength/aerobic improvements following our intervention, and thus we are building on our success to target a novel subclinical endpoint to reduce*

cancer-related morbidity and mortality. This data will directly inform a competitive R01 application using this clinical target to reduce cancer burden in endometrial cancer survivors.

3. Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
-To evaluate changes in PWV following a 12-week home-based aerobic and muscle strengthening exercise program	-Within participant change from pre- to post-intervention as measured by carotid-femoral pulse wave velocity (PWV)
Secondary	
To evaluate changes in FMD following a 12-week home-based aerobic and muscle strengthening exercise program	-Within participant change from pre- to post-intervention as measured by brachial artery flow mediated dilation (FMD)
-To evaluate changes in the modifiable components of the ASCVD risk score (total cholesterol, HDL cholesterol, triglycerides, and systolic blood pressure) following the 12-week home-based comprehensive exercise program	-Within participant change of total cholesterol, HDL cholesterol, triglycerides, and systolic blood pressure from pre- to post-intervention
Exploratory	
-To evaluate changes in functional fitness	-Within participant change of functional fitness from pre- to post-intervention as measured by the Functional Fitness Test
-To estimate muscle strengthening exercise session adherence	-Proportion of planned exercise sessions in which a participant completes at least 50% of prescribed exercises
-To estimate adherence to the aerobic physical activity guidelines (150 minutes/week)	-Proportion of planned weeks a participant accumulates 150 minutes of moderate intensity activity per week
-To estimate tele-coaching adherence	-Proportion of planned coaching sessions in which a participant completes
-To estimate acceptability	-Likert scale ratings of quality of exercise equipment, educational materials, health coaching, study feedback and distance delivery format
-To estimate changes in anthropometrics	-Within participant changes of waist and hip circumference, and weight from pre- to post-intervention
-To estimate changes in ambulatory activity levels	-Within participant change in average daily steps taken within a week from pre- to post-intervention as measured via ActiGraph accelerometer
-To estimate changes in psychosocial behavior change measures	-Within participant change of questionnaire scores (SEE, BPNES, PSS, BREQ-3) from pre- to post-intervention
-To estimate changes in diet	-Within participant change of questionnaire score (Multifactor Screener in Observing Protein and Energy Nutrition (OPEN)) from pre- to post-intervention
-To evaluate changes in the short performance physical battery (SPPB)	-Within participant change from pre- to post-intervention as measured by the SPPB

4. Study Population

This is a single arm project with no control group. We will recruit from the gynecologic oncology clinic at the University of Iowa Holden Comprehensive Cancer Center. In collaboration with the gynecologic oncologists including Dr. Michael Goodheart, we will recruit patients who meet our inclusion criteria (outlined below) and who do not meet our exclusion criteria (listed below). Alyssa Noble will be the primary research coordinator recruiting participants in clinic for this study. As we intend to study adults, participants include subjects of at least 18 years of age or older, who are medically able to safely participate in adopting a new exercise regimen.

In addition, we will recruit individuals from the Iowa Cancer Registry based on date of diagnosis, histology, cancer stage, and sex. Researchers from the ICR will send out recruitment letters for individuals to release their contact information. The mailing will provide a brief explanation of the study as well as the how and why their contact information would be shared if they consent to release their information. Information from individuals who provide their consent to release will be shared with our study team via secured platforms to contact for eligibility and screening. These individuals will be contacted via telephone to be given a more detailed explanation of the study following a standardized script to be further screened for meeting our inclusion criteria. Alyssa Noble will be the primary research coordinator screening and recruiting patients via telephone for this study.

4.1 Inclusion criteria

Inclusion Criteria	
1	Willing and able (cognitively and intellectually) to provide written informed consent
2	Willing to comply with all study procedures and be available for the duration of the study
3	Fluent in spoken and written English
4	Women ≥18 years of age
5	Documented diagnosis of Type I, stage I-IIIc endometrial cancer within the past 5 years
6	Completion of current cytotoxic treatment for endometrial cancer
7	Technology access (phone call access, broadband internet, Wi-Fi) for tele coaching
8	Comfort and willingness to use technology (videoconferencing) throughout the study for coaching
9	Pass the Physical Activity Readiness Questionnaire (PAR-Q)
10	Medical clearances given by their primary provider / oncologist (if indicated by the PAR-Q)

4.2 Exclusion criteria

Exclusion Criteria	
1	Absolute contraindications to exercise (i.e., acute myocardial infarction, severe orthopedic or musculoskeletal limitations)
2	History of previous myocardial infarction, ischemia, or hemorrhagic stroke
3	Medically documented history of heart disease including heart valve disease, coronary artery disease, heart failure, peripheral artery disease, aortic disease, pericardial disease, cerebrovascular disease, or deep vein thrombosis
4	Medical documentation of treatment-resistant hypertension OR taking 3 or more anti-hypertensives with persistent hypertension
5	Medically documented history of cardiovascular disease including (but not limited to): bypass surgery, stent procedures, bypass grafts, or coronary angioplasty

6	Medically documented or self-reported type 1 diabetes (insulin-dependents)
7	Prescriptions for or use of semaglutide (GLP-1 agonists) including name brands: Ozempic, Wegovy or Mounjaro
8	Current or recent (within last 3 months) use of hormone replacement therapy (HRT)
9	Evidence of recurrent or metastatic disease
10	Currently performing resistance training ≥2 days per week
11	Currently exceeding 150 minutes of at least moderate intensity exercise per week
12	Report of chest pain, shortness of breath, fainting, or angina pectoris
13	Self-reported history of falling, fall risk
14	Have physical disability that would limit range of motion through exercises such as sitting, standing and inability to walk one block
15	Plans to move from the area
16	Enrolled in another clinical trial or has used of any investigational drugs, biologics, or devices within 30 days prior to study enrollment
17	Self-reported tobacco use in last 7 days, current smoking, current tobacco use including e-cigarettes and vaping devices
18	Not suitable for study participation due to other reasons at the discretion of the investigator

5. Study Design and Methods

5.1 General Design

- A single arm exercise study
- The intervention itself is 12 weeks of exercise, with one week of accelerometer wear prior to exercise with an additional week to schedule post-study visit procedures, yielding a total intervention length of 14 weeks.
- The exercise intervention will consist of (a) in-person pre-intervention study measures; (b) instructional materials (e.g. detailed exercise manual) and exercise training equipment (e.g. resistance bands, adjustable pair of dumbbells, Fitbit Charge 5); (c) a virtually delivered instructional session; (d) access to informational web materials; (e) support and feedback provided via virtual health coaching sessions; and (f) in-person post-intervention study measures. Participants will also receive access to a study specific website (strivecardio-study.lab.uiowa.edu) that will include online versions of resources including video demonstrations, device support, exercise recommendations and study components.
- Health coaching sessions will be delivered virtually and consist of (a) an initial health coaching session during week one discussing the participant's visions for health and wellness and overall goals of completing the intervention exercises; (b) sessions delivered once per week through week four discussing progress, barriers, facilitators, self-efficacy, and motivations for exercise goals to facilitate exercise adoption; (c) a midpoint check-in including a non-bias report from their health coach describing their progress thus far in the intervention. Participants then have the personal option to continue meeting with their health coach on a weekly basis or taper their health coaching sessions to include only weeks eight and eleven; (d) a final in person health coaching session to conclude.

6. Study Procedures

All participants will be asked to meet with the research team in-person at the University of Iowa Physical Activity and Cancer Survivorship (PACS) Lab in room 127 Iowa Bioscience Innovation Facility (IBIF) in a fasted state. Participants will be asked to bring a snack/food that can be refrigerated/stored in the lab after physiologic procedures. During the in-person visit in the PACS lab, participants will complete informed

consent from the study coordinator. After which, they will be escorted to the University of Iowa Clinical Research Unit (CRU) located in General Hospital 2 Boyd Tower at the University of Iowa Health Care main campus. While at the CRU participants will undergo described cardiovascular measurements by a trained technician before being escorted to the PACS Lab to break their fast to consume their snack/food, and then complete remaining described study protocols, and baseline assessments. They will also receive an ActiGraph accelerometer to wear for a seven-day wear protocol and then charge the device at home. They will also receive a Fitbit device and will receive instruction on how to use. Each participant will be asked to repeat the wear protocol week 12 of the study. These specific measures are described below. After completion of study baseline measures, participants will undergo an instructional session to the exercise program described below in **section 6.2.**

Calendar/Schedule of events

Measure	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Final Visit
Informed Consent	X													
Carotid-femoral pulse wave velocity	X													X
Brachial artery flow mediated dilation	X													X
Blood draw	X													X
Demographics / health history	X													
Self-efficacy for exercise surveys (2)	X													X
Psychosocial behavior change questionnaires	X													X
OPEN questionnaire	X													X
Anthropometrics	X													X
Functional fitness	X													X
SPPB	X													X
Device orientation (Fitbit/telecoaching)	X													
ActiGraph accelerometer	X												X	
Exercise instructional session	X													
Telehealth meetings: *Weekly option*	X	X	X	X	X	X	X	X	X	X	X	X		
Telehealth meetings: *Tapered option*	X	X	X	X	X	X			X			X		
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence		X	X	X	X	X	X	X	X	X	X	X	X	X
Acceptance/satisfaction survey														X

6.1 Study measures

Below are the study measures that will be collected over the study period:

Anthropometrics and resting cardiovascular measures: Height, weight, waist and hip circumferences will be measured using standard protocols by a research team member in the CRU. Resting heart rate

and blood pressure will be measured by a trained technician in the CRU using standard protocols. When collected: Baseline, final visit (~12 weeks)

Blood based biomarkers: Participants will have blood drawn by trained clinicians within the Clinical Research Unit (CRU) including total cholesterol, high-density lipoprotein, low-density lipoprotein, glucose, triglycerides, and insulin. Vitals: Participants will have their heart rate and blood pressure measured. When collected: Baseline, follow-up (~ 12 weeks).

FMD. Endothelial function will be tested via a non-invasive procedure in the Vascular Physiology Assessment core lab at the CRU. This is a commonly used non-invasive assessment of vascular endothelial function and biomarker of cardiovascular disease risk. The test is performed by a trained researcher using a high-resolution ultrasound machine (Logiq e9, GE Healthcare) to obtain measures of the brachial artery diameter and blood flow at rest. The forearm is then occluded with a supra-systolic blood pressure cuff placed on the forearm for five minutes followed by immediate release. The artery diameter and blood flow are imaged again immediately after the sudden release of the cuff for 2 minutes to capture the vasodilation that occurs. The percentage dilation of the brachial artery (8-10% in normal, healthy adults) is measured off-line with image detection software (Vascular Analysis Tools, Medical Imaging Applications, LLC) and the magnitude of increase in blood flow (called reactive hyperemia) are recorded and increase the blood flow velocity or shear rate (=blood flow velocity/diameter) are used to quantify the “shear” stimulus for dilation.

Aortic stiffness. After a minimum of 5 minutes rest, three BPs are taken using the NIHem Workstation (Cardiovascular Engineering, Inc) two minutes apart. The research participant will be instrumented with a small finger cuff that will continuously record blood pressure in the finger. Carotid-femoral artery PWV, the ‘gold standard’ in vivo assessment of aortic stiffness in humans, will be assessed by applanation tonometry using the Sphygmocor pulse wave analysis system (AtCor Medical, Inc.) as previously described[24]. After 10 minutes of supine rest, carotid, brachial, and femoral artery pulse waveforms will be recorded non-invasively by sequentially recording of carotid, brachial, and femoral artery pulse waveforms with a hand-held transducer for 20 seconds. Pressure waveforms are gated to the 13 lead ECG R wave in order to calculate the transit time (t) between the foot of the carotid and the femoral waveforms. The carotid-femoral and carotid-brachial transit distance (CFTD) is estimated between the 2 anatomical sites as the difference between the suprasternal notch (SSN) to carotid (SSN-C) and femoral (SSN-F) sites. Thus, the CFTD=(SSN-F)-(SSN-C) and PWV calculated as CFTD/t. This approach accounts for parallel transmission of the pulse wave up the brachiocephalic and carotid arteries, and simultaneously along the aortic arch using the SSN as a fiducial point where parallel transmission begins (e.g., bifurcation site of aortic arch/brachiocephalic artery).

Carotid artery compliance/stiffness will be determined noninvasively by high-resolution ultrasonography (Logiq 7, GE Healthcare) of the right common carotid artery and contralateral assessment of carotid artery blood pressure via non-invasive carotid artery applanation tonometry, respectively. Carotid artery diameters are measured ~2 cm proximal to the carotid bulb with the transducer placed at a 90° angle to the vessel by off-line analysis of DICOM images with image analysis software (Medical Imaging Applications, LLC). Maximal diameters (i.e., systolic expansion) and minimal diameters (e.g., diastolic relaxation) are measured in sync with carotid artery blood pressure waveforms. Carotid blood pressure waveforms are calibrated using diastolic and mean brachial artery blood pressure obtained from standard brachial artery cuff blood pressure.[25]

Accelerometer. Although participants will have a Fitbit for self-monitoring, we will use a research grade device to determine ambulatory activity levels at the beginning and end of the study. At the baseline visit, participants will be asked to wear the ActiGraph wGT3X-BT accelerometer (ActiGraph, Pensacola, FL) for 7 days during all waking hours. They will then be asked to keep the

device at home, charge it, and then will repeat this wear protocol on week 12 of the study. Participants will be instructed to notify (via call or email) the research staff once the baseline ActiGraph wear has been completed. ActiGraph is a gold standard method of objective activity assessment.[26, 27] In advance of the final week of the protocol participants will be asked to re-wear the ActiGraph device and bring the device and associated wear logs back to the final study visit. **When collected:** Baseline pre-intervention, last week of the intervention (~12 weeks)

Demographics and health history. At baseline, participants will be asked about sociodemographic factors, self-reported health history, cancer history will be abstracted from their medical records. In order to corroborate medical information for those coming from the Iowa Cancer Registry, we will be requesting relevant medical records from the participant's local oncologist or medical provider. The request will be sent in HIPPA compliant manner using a fax machine only accessible by the Principal Investigator. These questions will be collected from/stored on our secure REDCap database. **When collected:** Baseline

Self-efficacy for exercise surveys. At baseline and at follow-up, participants will be asked to complete two versions of the self-efficacy for exercise (SEE) scale. This 9-item survey will ask about self-efficacy (or confidence) related to aerobic exercise and then about muscle strengthening exercise. We will administer these two surveys at baseline and then at the end of the study as modality-specific measures of self-efficacy. **When collected:** Baseline, final visit (~14 weeks)

Autonomy, competence, and relatedness towards exercise survey. At baseline and follow-up, participants will be asked to complete the Basic Psychological Needs in Exercise Scale (BPNES). This 11-item survey will ask about feelings of autonomy, competence, and relatedness towards exercise in general as opposed to a specific situation. We will administer this survey at baseline and again at the end of the study as a measure of psychosocial needs with exercise. **When collected**: Baseline, final visit (~14 weeks)

Perceived social support survey. At baseline and follow-up, participants will be asked to complete the Multidimensional Scale of Perceived Social Support (PSS) survey. This is a 12-item survey identifies the source of social support identified by participants. Particularly from friends, family, or a significant other. We will administer this survey at baseline and again at the end of the study as a measure of social support. **When collected:** Baseline, final visit (~14 weeks).

Exercise regulations questionnaire. At baseline and follow-up, participants will be asked to complete the Exercise Regulations Questionnaire (BREQ-3). This 24-item survey will address the participant's underlying reasons for engaging or not engaging in exercise. We will administer this survey at baseline and again at the end of the study as a measure of motivation for exercise. **When collected:** Baseline, final visit (~14 weeks).

Multifactor Screener questionnaire. At baseline and follow-up, participants will be asked to complete the Multifactor Screener in Observing Protein and Energy Nutrition questionnaire. This 16-item survey will approximate intakes of fruits and vegetables, percentage energy from fat, and fiber. The screener asks participants to report how frequently they consume foods in 16 categories. We will administer this survey at baseline and again at the end of the study as a measure of fruit and vegetable intake, percent of calories from fat, and fiber. **When collected:** Baseline, final visit (~14 weeks).

Functional fitness. The functional fitness test (FFT) is a battery of seven tests measuring strength, flexibility, fitness, body composition, and agility. It has high test-retest reliability and is suitable for tracking within-person changes.[31] The functional fitness test battery includes the following 6 assessments: 1.) **The 30 second chair stand**, which assesses the strength of the lower body. Each person will have 30 seconds to stand up and sit down from a chair as many times as possible within the time frame. 2.) **The 30 second arm curl** assesses the strength of the upper body, where

women will hold a 5-pound dumbbell in a seated position, and they will have 30 seconds to curl their arm and extend it as many times as possible within the time frame. 3.) The **6-minute walk test** measures the total distance that a person can quickly walk on a flat hard surface within a period of 6 minutes, using a 100ft length of distance. 4.) **The chair sit and reach** assesses lower body flexibility where the participant will sit in a chair, extend one leg in front of them and flex at the waist, reaching toward their toes, and we will measure the distance between their toes and fingers. 5.) **The 8-foot-up and go** is an assessment of speed agility and balance. With this assessment, the participant begins in a seated position, and will be timed for the duration it takes to rise from the chair, walk as quickly as possible around a cone 8 feet away from the chair, and return to a seated position. 6.) **The back scratch test** is an assessment of the flexibility of the upper body, where the person will be seated and one arm will be flexed behind the head, and the other arm will be extended behind the shoulder. The assessment measures the distance between the fingertips of both hands. 7.) The **handgrip dynamometer test** is an assessment of grip strength. In a seated position, participants will be handed the dynamometer and instructed to squeeze the handle as hard as possible to generate maximum force at the grip, while maintaining the elbow at a flexed 90 degree angle. The participant will receive three alternating tries with each hand. **When collected:** Baseline, final visit (~14 weeks)

SPPB. The short performance physical battery (SPPB) is a series of functional mobility assessments which measure balance, lower extremity strength, and fitness. Developed by the National Institute of Aging, the SPPB has clinically useful implications of predicting physical decline in older adults[35]. The full battery utilizes standardized scoring, for a minimum of 0 points, to a maximum of 12 points, and includes the following three subscales: 1.) **Balance.** Each participant will stand for 10 seconds with their feet together, 10 seconds with their feet placed semi-tandem, and a final 10 seconds with their feet fully tandem. Participants receive a score from 0-4, based on their ability to attempt each position. 2.) **Repeated chair stand**, measuring lower extremity strength. Participants will stand up and sit down five times as quickly as they can. Participants receive a score of 0-4, based on total duration it takes to complete five total repetitions. 3.) **Gait speed.** Each participant will walk to a line placed on the floor three meters away at their typical walking pace. Participants receive a score from 0-4, based on total duration of walking this distance. **When collected:** Baseline, final visit (~14 weeks).

Exercise adherence. Adherence to intervention exercises will be measured via detailed exercise logs. A participant needs to complete at least 50% of the prescribed exercises in a session to be considered adherent to the session. **When collected:** ongoing, logs will be completed throughout the intervention and submitted at the final visit. Additionally, we will be monitoring participant's Fitbit data via Fitabase over the course of the study to monitor total physical activity and minutes of strength training logged.

Health coaching adherence. Adherence to health coaching will be monitored by the health coach on a weekly basis. A health coaching will be considered complete if the participant attends and participates in the health coaching session. Health coaches will also record the modality in which the session was completed, as well as the duration of completed sessions in minutes. **When collected:** ongoing, health coaches will record in REDCap whether a health coaching session was completed or not following each scheduled session.

Acceptability. Participants will receive a satisfaction survey at the end of the study that will ask them to report on the relative satisfaction and importance of key intervention components. This questionnaire will include Likert scales rating core components of the intervention including the quality of the exercise equipment, educational materials, health coaching, study feedback, and distance-delivery format. **When collected:** Final visit (~12 weeks)

Adverse Event Assessment. The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to grade adverse events. Subjects enrolled in this study will be evaluated for adverse events, serious adverse events, and adverse events requiring interruptions, modifications of discontinuation of the intervention. **When collected:** Baseline, and weekly (Weeks 1-12)

6.2 Exercise Familiarization

During the baseline visit, the study team will help the participant set up and activate their Fitbit device and account. They will also be oriented towards the basic functions of the Fitbit, demonstrating how to track one's steps and sync with their phone app. During the first week of participant accelerometer wear, following completion of informed consent and described baseline measures, participants will be given an exercise orientation and instructional visit virtually instructed by their designated health coach. The purpose of this session is for the participants to learn the exercise components of the intervention and understand how to safely use the equipment provided to them during their baseline visit. The instructional visit includes going through each exercise of the intervention (see Table below) to learn the movement, learn the muscle groups involved, and to learn how to monitor themselves by tracking their progress via logs. Each participant will receive a recommended starting point for each exercise with respect to intensity and progressions/regressions. For example, a participant may be starting on a blue resistance band for biceps curls, but the squats may simply be body weight at this time. Table 2 outlines the exercises for the intervention.

Table 2. Series of exercises, with progressions and regressions to increase/decrease difficulty.

Primary muscle group	Exercise	Progressions	Regressions
Thighs (quadriceps, hamstrings)	Body weight squats	• Add resistance band • Holding dumbbells	• Chair squats • Shortened range of motion
Calves (gastrocnemius, soleus)	Standing heel raises	• Holding dumbbells • Elevate ball of foot	• Shortened range of motion
Chest (pectoralis major & minor)	Standing chest press	• Increase band tension	• Reduce band tension
Back (trapezius, latissimus dorsii)	Seated banded row	• Standing row • Increase band tension	• Reduce band tension • Shorten range of motion
Abdominals (rectus & transverus adbominus)	Static v-sit hold with feet on floor	• Elevate feet • Add rotation • Add dumbbell	• Support with hands • Add lumbar support w/ towel
Shoulders (deltoids)	Seated banded press	• Standing • Use dumbbells	• Reduce band tension • Shorten range of motion
Biceps brachii	Seated banded curl	• Standing • Add tension to band • Use dumbbells	• Reduce band tension • Shorten range of motion
Triceps brachii	Seated arm extension	• Increase band tension	• Reduce band tension

6.3 Exercise intervention

During the study period, participants will be instructed to complete the muscle strengthening exercise routine twice a week for 12 weeks during the intervention, and to monitor one's total steps and active minutes. Personalized aerobic activity goals will be set and monitored via health coaches on the research study team. Participants will be assigned a study coordinator/health coach who will work with each participant over the course of the intervention. Study coordinators/health coaches will schedule weekly telehealth meetings with the participants for the first five weeks of the intervention, following the fifth week participants will be given the choice to continue meeting with their study coordinator/health coach weekly or transition to a tapered telehealth session schedule where they will meet with their study coordinator/health coach again during week 8 and week 11. At these health coaching sessions, a semi-standardized template will be used. Study coordinators will check in to determine study progress, help set and monitor exercise goals, systematically evaluate for adverse events, and will work to build rapport and support the participants on their exercise adoption and maintenance journey. Study coordinators/health coaches will also be instructed to assess for volume/intensity/difficulty of each of the exercises. These

sessions are done over video so that the coordinator can build rapport with participants, and that participants can show or demonstrate issues with exercises or their form. Participants will have access to a study-specific website with resources related to exercise prescription and exercise components (strivecardio-study.lab.uiowa.edu).

7. Statistical Considerations

7.1 Statistical Methods

The primary objective of this pilot study is to obtain preliminary evidence of changes in PWV with the comprehensive exercise program. A 1 m/sec decrease in PWV from pre- to post-intervention reflects a clinically relevant change as this has previously been shown to be associated with a 15% risk reduction in CVD events. In statistical terms, we are testing the null hypothesis H_0: $\Delta_{Post\text{-}Pre} = 0$ versus the alternative hypothesis H_1: $\Delta_{Post\text{-}Pre} \neq 0$. Using a repeated measures design with 1 within subject factor (time: pre- and post-intervention), the design achieves 93% power to test for a time effect among 30 participants. We will recruit 33 participants to account for a potential 10% dropout rate to accommodate a final analytic sample size of 30. Power calculations are based on the following assumptions: standard deviation of 1.4, using an F test, 5% significance level, an autocorrelation of 0.5, and 15% drop out.

7.2 Statistical Analysis

7.2.1 General Approach

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by count and proportion.

7.2.2 Analysis of Primary Endpoint(s)

PWV

The within patient change in PWV will be assessed from pre- to post-intervention. Mixed effects regression models will be used to estimate changes in PWV. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

7.2.3 Analysis of Secondary and Exploratory Endpoint(s)

FMD

The within patient change in FMD will be assessed from pre- to post-intervention. Mixed effects regression models will be used to estimate changes in FMD. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

ASCVD Risk

The within patient change in the modifiable components of the ASCVD Risk score (total cholesterol, HDL cholesterol, and systolic blood pressure) will be assessed from pre- to post-intervention. Mixed effects regression models will be used to estimate changes in total cholesterol, HDL cholesterol, and

systolic blood pressure. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

Functional Fitness

Mixed effects regression models will be used to estimate changes in each of the 6 tests included in the Functional Fitness Test from pre- to post-intervention. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

Muscle Strengthening Exercise Session Adherence

Exercise session adherence will be defined as the proportion of planned exercise sessions in which a participant completes at least 50% of the prescribed exercises. The mean and associated 95% confidence interval will be reported.

Aerobic Physical Activity Adherence

Aerobic physical activity adherence will be defined as the proportion of planned weeks a participant accumulates 150 minutes of moderate intensity activity. The mean and associated 95% confidence interval will be reported.

Tele-Coaching Adherence

Tele-coaching adherence will be defined as the proportion of planned exercise sessions in which a participant completes. The mean and associated 95% confidence interval will be reported.

Acceptability

Acceptability will be assessed using Likert scale ratings of quality of exercise equipment, educational materials, health coaching, study feedback and distance-delivery format. Means and associated 95% confidence intervals will be reported for each item.

Anthropometrics

The within patient change of weight, waist and hip circumferences will be assessed from pre- to post-intervention. Mixed effects regression models will be used to estimate changes in anthropometrics. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

Ambulatory Activity Levels

The within patient change in average daily steps taken within a week will be assessed from pre- to post-intervention. Mixed effects regression models will be used to estimate changes in ambulatory activity levels. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean and associated 95% confidence interval will be reported.

Psychosocial Behavior Change

The within patient change in psychosocial behavior will be assessed from pre- to post-intervention. The SEE, BPNES, PSS, and BREQ-3 self-report questionnaires will be used to assess psychosocial behaviors. Mixed effects regression models will be used to estimate changes in questionnaire scores. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean and associated 95% confidence interval will be reported.

SPPB

Mixed effects regression models will be used to estimate changes in each of the three tests included in the SBBP from pre- to post-intervention. We will follow standardized SPPB scoring for each of the three tests, with each individual test score ranging from 0-4. A total sum score for the entire battery of 0-12 will also be measured. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean changes and associated 95% confidence intervals will be reported.

OPEN questionnaire diet change

The within patient change in dietary composition will be assessed from pre- to post-intervention. The OPEN questionnaire will be used to assess changes in fruits, vegetables, percent energy from fat, and fiber. Random effects will be included to account for the longitudinally correlated nature of repeat measurements within a patient. Estimated mean and associated 95% confidence interval will be reported.

7.2.4 Safety Analyses

The incidence of treatment-emergent adverse events will be summarized by system organ class and/or preferred term, type of adverse event, severity (based on NCI CTCAE v5.0 grades), and relation to study treatment. The most severe grade per patient will be reported.

7.2.5 Planned Interim Analyses

There are no planned interim analyses.

1. Data Collection and Record Keeping

8.1 Data Confidentiality

We will take extensive measures to ensure data safety and security. A dedicated study database will be constructed on a secure server using the Oncore study management system.

8.2 Data Capture

To ensure the integrity of the data collected from study participants, several procedures will be implemented. All personnel involved in data collection will be thoroughly trained in all assessment methods, thus ensuring consistent applications of procedures and measurement consistency across participants. All data will be saved to a computer hard drive-in real time and then stored on a secure server (i.e., password protected) which is backed up daily. All raw data will be kept electronically within REDCap on a server maintained by the Holden Comprehensive Cancer Center. Informed consent forms will be kept in hard copy format in a locked file cabinet with restricted access. Issues related to

data integrity will be discussed on a weekly basis as a recurring agenda item in the weekly project meeting. Finally, continuing review of all procedures will be obtained by all appropriate institutional review boards.

Study data will be labeled with a study ID number. Data linking the study ID numbers with subject identities will be stored in hard copy format only. This and other paper files will be kept in a locked file cabinet in the Physical Activity and Cancer Survivorship (PACS) Lab (Room 127 Iowa Bioscience Innovation Facility (IBIF), 115 S Grand Ave, Iowa City, IA 52245). Only study personnel will have access to participant data if necessary for research duties. Electronic data, including accelerometer data files, will be kept on a server maintained by the Holden Cancer Center, in a drive accessible only by the PI and study staff. Data will be retained for an indefinite amount of time, and all study data will be banked in a coded format. Data may be used in the future for a secondary data analysis looking at relationships between collected study data and other variables. Study data may only be used by the study team, and all future investigations using any data from this study must undergo a separate IRB application. Use of study data is limited to the research team for this protocol unless a separate IRB application is submitted for use of this banked data for future investigations.

8.2.1 Fitbit and Fitabase

Fitbit Charge 5 will be provided to all participants in the study. The *Charge 5* is not intended to be used as a medical device. All participants will have the ability to monitor physical activity, sleep, and heart rate with the Fitbit ***Charge 5.*** All data from the Fitbit ***Charge 5*** will be continuously streamed to the Fitbit servers, and then pulled into the Fitabase data aggregator.

We have applied several data use limitations to respect the privacy and autonomy of research subject's data, including minimizing collection and use of personal data, meaning data that directly identifies an individual, or that could reasonably be linked to an individual by an anticipated data recipient. Participants will create their Fitbit accounts using coded, de-identified information with all fields that could directly identify them removed. After study completion, we will permanently delete these accounts but allow individuals to create their own personal Fitbit accounts that are not linked to us or the study in any way.

We do not use or share with third parties any personal data for new research studies, or for any purpose different from the original study purposes.
We will implement mandatory training for researchers on applicable privacy standards, and data protection impact assessments as appropriate or required by law.
We will never use personal data in a way that is likely to cause damage or distress to research subjects.
We will never sell the personal data of research subjects. We will never use it for advertising, marketing, re-identification, adverse decisions about employment or insurance, or any data mining or analysis for purposes other than necessary for research purposes.
We also plan to use best practices for de-identification include:

- Providing summary-level aggregate data rather than individual-level de-identified data.
- We also will give research participants control over their personal data. Research participants must have the ability to withdraw at any time from the research study, which should include an option to delete their personal data or, at a minimum, remove it from future research studies.
- We will maintain data security by using technical, administrative, and physical controls that are appropriate to the sensitivity of the data, meet or exceed industry standards, and are reasonably designed to protect against unauthorized access, use, or disclosure of the data. The following strategies will be deployed: data encryption, access controls, logging, auditing, confidentiality requirements, data use policies (including incident response and breach notification plans, as applicable), and training.

9 Study Finances

This work was supported by Grant IRG-21-141-46-IRG from the American Cancer Society, administered through the Holden Comprehensive Cancer Center at The University of Iowa (PI: Gorzelitz).

9.1 Subject Stipends or Payments

Participants will be paid $50 in cash at the baseline visit as well as another $50 cash at the final (post-intervention) visit. Those who complete the intervention will receive a total of $100 cash, in addition to keeping their exercise equipment of the resistance bands and dumbbells. All participants will also be allowed to keep the Fitbit used during the study.

10. Risks and Benefits

10.1 Direct benefits.

There are no direct benefits to individuals expected because of participating in this trial.

10.2 Potential Benefits of the Proposed Research to Human Subjects and Others.

Findings from the proposed study will contribute to the scientific knowledge of the feasibility of home-based exercise interventions in endometrial cancer survivors. Additionally, the knowledge gained will contribute to the scientific knowledge aimed at understanding the potential therapeutic benefits of resistance training exercise for endometrial cancer survivors. The risks of our study procedures are low and therefore are seen as justifiable regarding the knowledge to be gained.

10.3 Importance of Knowledge to be gained.

Increasing physical activity after a cancer diagnosis is an important area of researching and finding feasible interventions for endometrial cancer survivors are key to sustainable lifestyle changes. This research will evaluate the changes in cardiometabolic risk in this population following our exercise intervention, and take the first step that will provide valuable information and serve as a scaffolding for the continued design and development of future interventions.

10.4 Most common or frequent physical risks expected.

Potential risks of participating in this study include pain or bruising from blood draw, pain from endothelial function test, acute injury, musculoskeletal soreness. Risks/discomfort of the physical testing at baseline/follow up include acute injury, musculoskeletal soreness from some of the assessments. We have minimized these risks as much as possible, described below.

10.5 Potential long-term risks.

There are currently no known rare, serious risks related to exercise that are not listed above. Participants could suffer an acute musculoskeletal injury because of exercise, but individuals can recover from those events, although they are not good events.

10.6 Minimizing risk.

The aforementioned risks will be minimized in the following ways:

10.6.1 Risk of blood draw.

Potential risks associated with obtaining blood samples are minimal but include slight bruising, pain, a temporary feeling of faintness, and/or a small risk of infection. All blood draws will be performed by a research nurse at the CRU, trained in drawing blood. Only appropriate trained laboratory personnel perform the blood draw procedure. A sterile gauze pad and pressure wrap (latex free coban) are applied to the site after the blood draw to stop any bleeding and minimize bruising.

10.6.1 Risk of endothelial function test.
Common side effects include following the blood pressure cuff filling may cause a moderate intensity pain "pins and needles" or numbing sensation that goes away as soon as the cuff is deflated. We have minimized this risk as the procedure itself is noninvasive and should result in only little discomfort.

10.6.2 Risk of psychological distress.
This study poses low risk of psychological stress. Emotional or psychological distress will be minimized by having adequate recruitment criteria, in addition to having adequate informed consent to detail what participation includes. All the study questionnaires we are using are validated and appropriate measures, which do not ask about sensitive or stigmatizing topics. Finally, we will use adequate privacy and confidentiality measures.

10.6.3 Risk of musculoskeletal soreness/injury.
To avoid unsafe exercise in those who are not able to exercise, we will exclude individuals who report difficulty transitioning from sitting to standing, walking 1 block (as a proxy measure of basic physical functioning). Additionally, all participants must pass the validated Physical Activity Readiness Questionnaire (PAR-Q) prior to enrollment. Participants will be in regular contact with the study coordinator throughout the study. If any muscular or skeletal discomfort or soreness should develop, the study coordinator will reduce the intervention targets accordingly to resolve the discomfort. The prescription of resistance exercise is consistent with guidelines for cancer survivors on what is appropriate prescribed exercise including non-maximal intensity (both from the American Cancer Society and the American Council of Sports Medicine). Participants in the study will be given training on how to conduct the exercises, additionally they will have study staff to call in case of questions, additionally having access to resource videos and video-calls with staff. The use of safe and proper form will be stressed at all interactions to increase efficacy of exercises and reduce the risk of injury. Participants will also be instructed to exercise on non-consecutive days to allow the body to recover. While risk of injury or soreness can never be fully prevented, these steps will maximize the risk reduction.

10.6.4 Risk of loss of confidentiality.
We will take extensive measures to ensure the safety and security of participant data. OnCore data recording will be completed as required. All study staff will complete IRB/HIPAA training prior to having contact with participants or with study data. Paper files (i.e. informed consent documents) will be kept in a locked file cabinet in the PI's lab in the Fieldhouse (115 S Grand Ave, Iowa City IA 52240). The office door is kept always locked.

10.6.5 Risk related to study measures.
The Functional Fitness Test (FFT) and Short Performance Physical Battery (SPPB) are standardized protocols for older adults, and certain criterion are in place to minimize risks including only conducting the tests on those with non-hypertensive resting blood pressures, only conducting on those who are low fall risk, and using safeguards such as cuing breathing during the 30 second chair stand test and 30 second arm curl. For the six-minute walk test and three meter gait speed assessment, participants will walk along a hallway with a handrail to reduce risk of falling.

11. Adverse events and stopping criteria

Discontinuation of the exercise protocol is based on the discretion of the PI.

Any individual may self-discontinue the exercise program at any time. There are currently no prespecified stopping rules for the exercise program.

12. Appendix

Appendix 1: Muscle strength Exercise tracking log (example) for week 1 of 12 weeks

Participant ID: **STRENGTH EXERCISE LOG**

WEEK OF INTERVENTION: 1 Dates: _____/_____/_____ - _____/_____/___ **Day (circle): 1 2 3 4**

Exercise	Equipment (Circle one)	Resistance	Set 1		Set 2		Set 3 (OPTIONAL)	
			Repetitions (max. 12)	RPE (1-10)	Repetitions (max. 12)	RPE (1-10)	Repetitions (max. 12)	RPE (1-10)
Squats	Body weight Band(s) Kettlebell							
Heel Raises	Body weight Band(s) Kettlebell							
Chest Press	Body weight Band(s) Kettlebell							
Back Row	Body weight Band(s) Kettlebell							
Shoulder Press	Body weight Band(s) Kettlebell							
Biceps Curl	Body weight Band(s) Kettlebell							
Triceps Extension	Body weight Band(s) Kettlebell							

Static V-Hold	Body weight Band(s) Kettlebell		Duration (seconds)	RPE (1-10)	Duration (seconds)	RPE (1-10)	Duration (seconds)	RPE (1-10)

Key for recording resistance when using the bands or kettlebell:

Band(s): Yellow Blue Green Black Red

Kettlebell: 8 12 16 20 24 28 32 36 40

QR CODE HERE

Appendix 2: Aerobic Exercise tracking log (example) for week 1 of 12 weeks

Participant: **AEROBIC EXERCISE LOG**

QR CODE HERE

WEEK OF INTERVENTION: 1 Dates: _____/_____/_____ – _____/_____/_____

Day of week	Light intensity		Moderate intensity		Vigorous intensity		Total daily steps (Fitbit)
	Activities	Total minutes	Activities	Total minutes	Activities	Total minutes	
Example	*Mall shopping*	*60*	*Walking the dog Bike ride*	*50*	*NONE*	*0*	*5,000*
1							
2							
3							
4							
5							
6							
7							

**Record aerobic activities under the best fit intensity and record the total minutes you spent in each intensity. For example, in one day if you spent 30 minutes walking the dog and later spent 20 minutes on a bike ride both activities would be recorded under moderate intensity and the total duration is 50 minutes.

Appendix 3: Physical Activity Readiness Questionnaire (PAR-Q) and You

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly:

YES	NO		
☐	☐	1.	Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2.	Do you feel pain in your chest when you do physical activity?
☐	☐	3.	In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4.	Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5.	Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7.	Do you know of any other reason why you should not do physical activity?

If you answered:

YES to one or more

Talk to your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want – as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- Start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- Take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

Delay becoming much more active:

- If you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- If you are or may be pregnant – talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional.
Ask whether you should change your physical activity plan.

Appendix 4: Demographic and health history questionnaire

Demographics and Medical History

Record ID	_____
Age	_____
Race	☐ American Indian/Alaskan Native ☐ Asian ☐ Native Hawiian/Pacific Islander ☐ Black/African American ☐ White
Ethnicity	◯ Hispanic or Latina ◯ Not Hispanic or Latina
How would you describe your current employment status?	◯ Full time ◯ Part time ◯ Retired ◯ On Disability ◯ Other
If other employment status, please list.	_____
How would you describe your highest level of education?	◯ Some high school ◯ High school degree or completed GED ◯ Some college ◯ Associates degree or Trade School Degree ◯ Bachelor's degree ◯ Some graduate school ◯ Graduate school degree ◯ Other
If other education level, please list.	_____
How would you describe your current relationship status?	◯ Single ◯ Married / Partnered ◯ Widowed ◯ Other
Is there currently anyone else living in your household?	◯ No ◯ Yes, an adult ◯ Yes, a child
Not including you, how many adults live in your household?	_____
How many children live in your household?	_____
Do you have any ongoing health concerns that may affect your ability to exercise? If yes, please list.	_____

Do you have any of the following health concerns?	☐ Asthma ☐ Blood Clots or Deep Vein Thrombosis ☐ Chest Pain ☐ Chronic Lung Disease ☐ Congestive Heart Failure ☐ COPD ☐ Diabetes ☐ History of a Heart Attack ☐ Heart Murmur ☐ High Blood Pressure ☐ Irregular/ Fast Heart Rate ☐ Multiple Sclerosis ☐ Osteoporosis ☐ Arthritis ☐ Osteoarthritis ☐ Parkinson's Disease ☐ Rheumatoid Arthritis ☐ History of a Stroke
Are you on any medications for hypertension?	◯ Yes ◯ No
What medications are you taking for your hypertension?	_____
Are you taking any statin medications for your cholesterol?	◯ Yes ◯ No
Which statins are you taking?	_____
Do you take Aspirin daily?	◯ Yes ◯ No
Do you have a history of falling?	◯ Yes ◯ No
How many times have you fallen in the last year?	_____
When was your last fall?	_____
Have you ever smoked any cigarettes?	◯ No ◯ Yes, but less than 100 in my lifetime ◯ Yes, but I quit ◯ Yes, and I currently still smoke
How long ago did you quit smoking?	_____
How many cigarettes do you smoke per day?	_____
Do you use any other tobacco products?	◯ Yes ◯ No

What type of tobacco product?	_____
How long have you been using that tobacco product?	_____
Do you use a vape or e-cigarettes?	◯ Yes ◯ No
How long have you been using a vape or e-cigarette?	_____
How many alcoholic drinks do you consume in an average week?	◯ None ◯ Less than 1 ◯ 1-3 ◯ 4-6 ◯ 7 or more

Appendix 5.1 Self-Efficacy for Exercise (SEE) Aerobic Scale

How confident are you right now that you could perform aerobic exercise three times per week for 20 minutes if:

	Not Confident										**Very Confident**
1. The weather was bothering you	0	1	2	3	4	5	6	7	8	9	10
2. You were bored by the program or activity	0	1	2	3	4	5	6	7	8	9	10
3. You felt pain when exercising	0	1	2	3	4	5	6	7	8	9	10
4. You had to exercise alone	0	1	2	3	4	5	6	7	8	9	10
5. You did not enjoy it	0	1	2	3	4	5	6	7	8	9	10
6. You were too busy with other activities	0	1	2	3	4	5	6	7	8	9	10
7. You felt tired	0	1	2	3	4	5	6	7	8	9	10
8. You felt stressed	0	1	2	3	4	5	6	7	8	9	10
9. You felt depressed	0	1	2	3	4	5	6	7	8	9	10

Appendix 5.2 Self-Efficacy for Exercise (SEE) Muscle strengthening Scale

How confident are you right now that you could perform muscle strengthening exercise three times per week for 20 minutes if:

	Not Confident										**Very Confident**
1. The weather was bothering you	0	1	2	3	4	5	6	7	8	9	10
2. You were bored by the program or activity	0	1	2	3	4	5	6	7	8	9	10
3. You felt pain when exercising	0	1	2	3	4	5	6	7	8	9	10
4. You had to exercise alone	0	1	2	3	4	5	6	7	8	9	10
5. You did not enjoy it	0	1	2	3	4	5	6	7	8	9	10
6. You were too busy with other activities	0	1	2	3	4	5	6	7	8	9	10
7. You felt tired	0	1	2	3	4	5	6	7	8	9	10
8. You felt stressed	0	1	2	3	4	5	6	7	8	9	10
9. You felt depressed	0	1	2	3	4	5	6	7	8	9	10

Appendix 6: Basic Psychological Needs in Exercise Scale (BPNES)

Instructions. The following sentences refer to your overall experiences **in exercise in general** as opposed to any particular situation. Using the 1-5 scale below, please indicate the extent to which you agree with these statements by circling one number for each statement.

	I don't agree at all	I agree a little bit	I somewhat agree	I agree a lot	I completely agree
1. I feel I have made a lot of progress in relation to the goal I want to achieve.	1	2	3	4	5
2. The way I exercise is in agreement with my choices and interests.	1	2	3	4	5
3. I feel I perform successfully the activities of my exercise programme.	1	2	3	4	5
4. My relationships with the people I exercise with are very friendly.	1	2	3	4	5
5. I feel that the way I exercise is the way I want to.	1	2	3	4	5
6. I feel exercise is an activity which I do very well.	1	2	3	4	5
7. I feel I have excellent communication with the people I exercise with.	1	2	3	4	5
8. I feel that the way I exercise is a true expression of who I am.	1	2	3	4	5
9. I am able to meet the requirements of my exercise program.	1	2	3	4	5
10. My relationships with the people I exercise with are close.	1	2	3	4	5
11. I feel that I have the opportunity to make choices with regard to the way I exercise	1	2	3	4	5

Autonomy: items 2, 5, 8, 11
Competence: items 1, 3, 6, 9
Relatedness: items 4, 7, 10

Appendix 7: Perceived Social Support (PSS) survey

Instructions: We are interested in how you feel about the following statements. Read each statement carefully. Indicate how you feel about each statement.

Circle the "1" if you **Very Strongly Disagree**
Circle the "2" if you **Strongly Disagree**
Circle the "3" if you **Mildly Disagree**
Circle the "4" if you are **Neutral**
Circle the "5" if you **Mildly Agree**
Circle the "6" if you **Strongly Agree**
Circle the "7" if you **Very Strongly Agree**

1.	There is a special person who is around when I am in need.	1	2	3	4	5	6	7	SO
2.	There is a special person with whom I can share my joys and sorrows.	1	2	3	4	5	6	7	SO
3.	My family really tries to help me.	1	2	3	4	5	6	7	Fam
4.	I get the emotional help and support I need from my family.	1	2	3	4	5	6	7	Fam
5.	I have a special person who is a real source of comfort to me.	1	2	3	4	5	6	7	SO
6.	My friends really try to help me.	1	2	3	4	5	6	7	Fri
7.	I can count on my friends when things go wrong.	1	2	3	4	5	6	7	Fri
8.	I can talk about my problems with my family.	1	2	3	4	5	6	7	Fam
9.	I have friends with whom I can share my joys and sorrows.	1	2	3	4	5	6	7	Fri
10.	There is a special person in my life who cares about my feelings.	1	2	3	4	5	6	7	SO
11.	My family is willing to help me make decisions.	1	2	3	4	5	6	7	Fam
12.	I can talk about my problems with my friends.	1	2	3	4	5	6	7	Fri

The items tended to divide into factor groups relating to the source of the social support, namely family (Fam), friends (Fri) or significant other (SO).

Appendix 8: Exercise Regulations Questionnaire (BREQ-3)

WHY DO YOU ENGAGE IN EXERCISE?

We are interested in the reasons underlying peoples' decisions to engage or not engage in physical exercise. Using the scale below, please indicate to what extent each of the following items is true for you. Please note that there are no right or wrong answers and no trick questions. We simply want to know how you personally feel about exercise. Your responses will be held in confidence and only used for our research purposes.

		Not true for me		**Sometimes true for me**		**Very true for me**
1	It's important to me to exercise regularly	0	1	2	3	4
2	I don't see why I should have to exercise	0	1	2	3	4
3	I exercise because it's fun	0	1	2	3	4
4	I feel guilty when I don't exercise	0	1	2	3	4
5	I exercise because it is consistent with my life goals	0	1	2	3	4
6	I exercise because other people say I should	0	1	2	3	4
7	I value the benefits of exercise	0	1	2	3	4
8	I can't see why I should bother exercising	0	1	2	3	4
9	I enjoy my exercise sessions	0	1	2	3	4
10	I feel ashamed when I miss an exercise session	0	1	2	3	4
11	I consider exercise part of my identity	0	1	2	3	4
12	I take part in exercise because my friends/family/partner say I should	0	1	2	3	4

13	I think it is important to make the effort to exercise regularly	0	1	2	3	4
14	I don't see the point in exercising	0	1	2	3	4
15	I find exercise a pleasurable activity	0	1	2	3	4
16	I feel like a failure when I haven't exercised in a while	0	1	2	3	4
17	I consider exercise a fundamental part of who I am	0	1	2	3	4
18	I exercise because others will not be pleased with me if I don't	0	1	2	3	4
19	I get restless if I don't exercise regularly	0	1	2	3	4
20	I think exercising is a waste of time	0	1	2	3	4
21	I get pleasure and satisfaction from participating in exercise	0	1	2	3	4
22	I would feel bad about myself if I was not making time to exercise	0	1	2	3	4
23	I consider exercise consistent with my values	0	1	2	3	4
24	I feel under pressure from my friends/family to exercise	0	1	2	3	4

Appendix 9: OPEN questionnaire

PART 1. Please think about what you usually ate or drank during the past month, that is, the past 30 days. Please read each question carefully and:

- **Report how many times per day, week, or month you ate each food.**
- **Choose the best answer for each question.**
- **Mark only one response for each question.**

1. How many times per **day**, **week**, or **month** did you **usually** eat **cold cereals**?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

2. How many times per **day**, **week**, or **month** did you use **milk**, either to drink or on cereal?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

2a. What kind of milk did you **usually** use? (Pick the one you used most often).

1. Whole milk
2. 2% fat
3. 1% fat
4. 1/2% fat
5. Non-fat or skim
0. DID NOT DRINK MILK IN PAST MONTH.

3. How many times per **day**, **week**, or **month** did you **usually** eat **bacon or sausage**, not including low fat, light, or turkey varieties?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

4. How often did you eat **hot dogs** made of beef or pork?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

5. How often did you eat **whole grain bread** including toast, rolls, and in sandwiches? Whole grain breads include whole wheat, rye, oatmeal, and pumpernickel.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

6. How often did you drink **100% fruit juice** such as orange, grapefruit, apple, and grape juices? Do **not** count **fruit drinks** such as Kool-Aid, lemonade, cranberry juice cocktail, Hi-C, and Tang.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

7. How often did you eat **fruit? Count** fresh, frozen, or canned fruit. **Do not count** juices.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

8. How often did you use **regular fat salad dressing or mayonnaise**, including on salad and sandwiches? Do **not** include low-fat, light, or diet dressings.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

9. How often did you eat **lettuce or green leafy salad**, with or without other vegetables?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

10. How often did you eat **French fries, home fries,** or **hash brown potatoes**?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

11. How often did you eat **other white potatoes**? **Count** baked potatoes, boiled potatoes, mashed potatoes, and potato salad. Do **not** include yams or sweet potatoes.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

12. How often did you eat **cooked dried beans**, such as refried beans, baked beans, bean soup, and pork and beans?

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

13. How often did you **usually** eat **other vegetables**?

COUNT:
- Any form of vegetable—raw, cooked, canned, or frozen.

DO NOT COUNT:
- Lettuce salads
- White potatoes
- Cooked dried beans
- Rice

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

14. How many times per **day**, **week**, or **month** did you **usually** eat **any kind of pasta**? **Count** spaghetti, noodles, macaroni and cheese, pasta salad, rice noodles, soba, and any other kind of pasta.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

15. How often did you eat **peanuts, walnuts, seeds,** or **other nuts**? Do **not** include peanut butter.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

16. How often did you eat **regular fat potato chips, tortilla chips, or corn chips**? Do **not** include low-fat chips.

☐	☐	☐	☐	☐	☐	☐	☐	☐
NEVER	1-3 times last month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 times per day	3 times per day	4 or more times per day

Appendix 10: Recruitment letter to be sent from the ICR

Date

Name
Address
City State, Zip

Dear Ms. Last Name,

We are writing to invite you to participate in a research study. The purpose of the study, conducted by the University of Iowa, is to measure changes in blood vessel health following a home-based exercise program in endometrial cancer survivors. A brochure with more details about the project is included with this mailing. We are contacting you to obtain consent to release your contact information to University of Iowa researchers so that they can talk with you more about their study.

Their study involves 12 weeks of exercising at home, with two visits to the University of Iowa at the beginning and end of the study. The researchers will provide you with weights and exercise bands – for you to keep – and ask you to complete two days each week of exercises that strengthen your muscles. They will also ask you to gradually increase your physical activity during the 12 weeks, with a goal of 150 minutes of total activity during week 12. You will be paid by the University of Iowa for participating in this research study. You will receive $100 for participating in this study. A $50 check will be mailed to the address you provide after the first in-person visit, and an additional $50 check will be mailed after the second in-person visit. If you choose to participate in the study, parking will be provided for both visits.

Every new diagnosis of cancer in Iowa is required by law to be reported to the Iowa Cancer Registry. The Iowa Cancer Registry gathers information about cancer diagnoses, patient survival, and treatment to help find causes of, and cures for cancer. We are reaching out to let you know about this opportunity to be part of a research study because your information is included in the Iowa Cancer Registry. Approximately 30 people, identified from both the Iowa Cancer Registry and from the Holden Comprehensive Cancer Center, will take part in this study at the University of Iowa.

If you agree to release your contact information to learn more about this study, please complete and return the form included in this mailing. Researchers from the University of Iowa will then contact you by phone to discuss the study. Sharing your contact information with University of Iowa researchers does not obligate you to participate in the research study, but will give you the opportunity to learn more about the study. Your decision to share your contact information will not affect any clinical care with which you may be involved. If you do not wish to participate, please return the form stating that you are not interested in learning more about the study. If we don't hear anything back from you, a reminder letter will be sent in two weeks.

We will keep the information you provide confidential, however federal regulatory

agencies and the University of Iowa Institutional Review Board (a committee that reviews and approves research studies) may inspect and copy records pertaining to this research. There are no known risks from being in this study, and you will not benefit personally. However, we hope that others may benefit in the future from what we learn as a result of this study.

You will not have any costs for being in this research study. Taking part in this research study is completely voluntary. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

If you have any questions about the research study itself, please contact **Jessica Gorzelitz; (319) 467-0849**. If you experience a research-related injury, please contact: **Jessica Gorzelitz; (319) 467-0849.** If you have questions about the rights of research subjects, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

Thank you very much for your consideration.

Sincerely,

Michele M. West, PhD
Coordinator of Special Studies
Iowa Cancer Registry

Sarah Nash, PhD
Director of Research
Iowa Cancer Registry

Jessica Gorzelitz, PhD
Principal Investigator
STRIVE Cardio Study

Appendix 11: Brochure included with ICR mailing

Who we are

Mission and Values

Our lab focuses on aerobic and muscle strengthening exercises for cancer survivors. Our mission is to use knowledge gained from research to help reduce treatment related symptoms, focus on health through strength, and improve the lives of cancer survivors.

Background of our work

We have previously established an exercise program for improving strength and aerobic fitness in endometrial cancer survivors. Now we would like to know how our exercise program may be able to improve the risk of developing cardiovascular disease in endometrial cancer survivors.

Purpose of our study

The purpose of our STRIVE Cardio study is to measure changes in blood vessel health and function after participants complete 12 weeks of exercises at home.

Meet our Study Team

Alyssa Noble
Our primary research assistant. Alyssa has great experience working with ovarian and endometrial cancer survivors at the University of Iowa for six years!

Jess Gorzelitz
Dr. Gorzelitz is the principal investigator of this study, and director of the Physical Activity and Cancer Survivorship Lab!

For more information about our STRIVE Cardio study, please complete and return the consent form included in your mailing!

Physical Activity and Cancer Survivorship Lab

You are invited to participate in our research study:

Measuring changes in blood vessel health and function following a home-based exercise program for endometrial cancer survivors

In this brochure you will find key information about this research study. Participating in this research study is completely voluntary. You do not need to take part in this study to continue receiving care for your condition. If you choose to participate, you may also discontinue at any time without penalty.

To learn more detailed information about the study, please complete the consent form included in your mailing. A research team member will contact you, and you may ask any questions you have about our study.

Main Study Procedures

This study involves an at-home exercise program that includes aerobic and muscle strengthening exercises with the support of a trained health coach for 12 weeks.

There will be two in-person study visits at the University of Iowa, each approximately 4 hours long. At these visits we will measure your endothelial function, vessel stiffness, cholesterol and blood sugar, aerobic capacity, strength, balance, agility, and flexibility. All measurements will be done at sub-maximal intensity.

We estimate participation in the study will last 14 weeks. When you begin, we ask you to wear a fitness device for one week. After you have worn that device for one week, you will begin the 12 weeklong at-home exercise program. After 12 weeks of exercising, we will work with your schedule for your second in-person study visit. Following this visit you will be done with the study, for a total of approximately 14 weeks.

Why you may or may not want to participate

We know from previous research in other cancer survivors that exercise is associated with improvements in endothelial function and blood vessel stiffness, along with better physical and mental health with lower risks of death. The Fitbit, dumbbells, and resistance bands will be yours to keep after your participation in the study.

You may choose not to participate due to the additional time needed for exercise, the additional study measures, or the need to come to the University of Iowa to complete in-person study measurements.

Risks and benefits

When starting new exercise movements, there is always a minimal risk of musculoskeletal injury or soreness.

You will not necessarily benefit directly from this study. We hope the findings of our research will help other endometrial cancer survivors in the future from the knowledge gained!

Appendix 12: Consent to release information included with ICR mailing

Consent for Release of Information

I authorize the release of my name, phone number, and address to researchers at the University of Iowa for measuring changes in vessel health following a home-based exercise program in endometrial cancer survivors. They will then contact me to provide more information regarding this study.

☐ YES, I am interested in learning more about the research study of the effect of combined aerobic and muscle strengthening exercises on structural and functional cardiovascular adaptations in endometrial cancer survivors. I authorize the release of my information to researchers at the University of Iowa.

My contact information is:

Name:_____

Address: _____

_____

Phone number: (cell) _____

(home) _____

☐ NO, I am not interested in learning more about this study. Do not release my information to the researchers at the University of Iowa.

Appendix 13: Screening script for screening ICR individuals via telephone

Hi my name is Alyssa. I am a research coordinator at the University of Iowa. I am calling because you gave permission to the Iowa Cancer Registry for us to call you to tell you about our reseach project. Do you have time now to discuss the study?

(If no,) Is there a time that would be better for me to call back?

(If yes, continue)
Our Study is a home-based exercise study for women who have completed treatment for endometrial cancer. This study is a 12-week cardio and strengthening exercise regimen to be done at home. The goal of this study is to measure improvements in your blood vessels, including stiffness and responsiveness and how that relates to overall health. We will also measure overall fitness including strength, agility and flexibility. Our staff will teach you how to do these exercises. You would be asked to come to the University of Iowa campus twice as part of this study, once at the beginning and again approximately 3 months later. You would be compensated $50 at each visit. All exercise and fitness tracking materials will be provided, including resistance bands, a kettlebell, and a Fitbit.

Right now for this study, we want to see if this program improves your cardiovascular health including the health and function of your blood vessels, so that we have the potential to roll this out to a larger population of endometrial cancer survivors. Your participation would help us determine that.

For research purposes, we will be measuring different aspects of your health and fitness at a pre-study assessment and again at a post-study assessment. At these assessments, we will be taking a blood draw to test for things like cholesterol and glucose. We will also conduct a carotid-femoral pulse wave velocity and brachial artery flow mediated dilation. Those are tests that measure artery health. Both are non-invasive and involve using ultrasound equipment to measure the time it takes for blood to travel through your body. The carotid-femoral pulse wave velocity will have a sensor on your neck and anther on your thigh. The brachial artery flow mediated dilation will have a sensor on your arm. The blood flow to your arm will be temporarily restricted using a cuff and then released. All of these tests will be conducted by a professional in the Clinical Research Unit which is located in this hospital. We will ask you to be fasted for these tests.

Once we finish at the CRU, we will run through a series of functional fitness tests. This is a set of nine low impact tests looking at your strength, flexibility, and agility. There's no running or heavy lifting.

At the end of the first assessment, you will be given exercise equipment and measurement tools. This includes resistance bands, an adjustable dumbbell, a Fitbit, and an accelerometer which is a pedometer that can also measure speed and distance. The first three will be for you to keep and the accelerometer we will need back at the end of the study. The Fitbit is for you to wear during the 12 weeks that you will be doing the exercises. We will get information from that Fitbit during that time. It comes straight to our account that we have set up for you. After the 12 weeks, you get to keep that Fitbit and we will turn over the account to you. We will not track your movement once the account goes to you. We will give you the login info and we recommend that you change it to whatever you would like.

Does all of that makes sense?

Now the final part of this study is weekly online coaching check-ins. We have a research assistant who will coordinate meeting times with you to see how you are doing. A change in routine like this can seem like a lot, so we want you to be able to have someone to discuss how things are going. If you like certain

exercises, or don't like others. If you have struggled with mastering an exercise, or if you made improvements and want to share the good news. That will be designated one-on-one time for you to discuss whatever aspects of the study you would like.

Do you have any questions about the study?

Does this sound like something you would be interested in doing?

(If no) Okay, thank you for your time. Have a great day!

(If yes) Great, I have a few eligibility questions I would like to discuss.
(Go through eligibility questions)

(If they fail) I'm sorry, unfortunately you are not eligible for this study. I appreciate the time you took to speak with me today.

(If they pass, continue)
You are eligible, which is great!
What I would like to do know is to go over the highlights of the consent. This is not a contract. It simply details all the information you would need for the study. You won't be signing this today. We will go over the important information together so you have a clear understanding of what will be happening before you come in for your first assessment. We will have you sign the consent at your first assessment when a study member can go over it with you.

(Go over the consent)

What I would like to do as the final step is to schedule your first assessment. As a reminder, you will have to come to the University of Iowa Health Care Medical Center, which is the main hospital in Iowa City. We would need you to be fasted, so it would be best to do this in the morning.

(Schedule visit)

Thank you so much for your time today. We will see you on (date and time). We will be emailing you instructions a few days in advance to remind you of everything you need to know and provide instructions for parking.

Do you have any questions?

If you think of any, please feel free to call me at any time.

Have a great day!

Appendix 14: Questionnaire for telephone eligibility screening

MEDICATIONS

Are you on any prescription medications?

List current medications:

Have you started any new medications in the last 3 months?

MEDICAL HISTORY

Do you have high blood pressure (aka, hypertension)?
Is your blood pressure well controlled?

Do you have diabetes? (If yes, ask questions below)
- **Do you take short-acting insulin?**
- **Do you take long-acting insulin? (If yes, ask questions below)**
  - **Have you been taking your long-acting insulin for more than 3 months?**

Other than endometrial cancer, have you been diagnosed with any other cancers? (If yes, ask questions below)
- **What treatment did you receive?**
- **How long ago did you complete treatment?**
- **What stage was your disease?**

In the past three months have you used any tobacco or nicotine products, such as cigarettes, e-cigs, vapes,? (If yes, ask questions below)
- **Are you currently using any nicotine or tobacco products?**
- **When was the last time you used one of these products?**

Do you currently have or have a history of any of the following conditions or diseases? Please listen to the entire list of conditions or diseases before answering YES or NO.

Brain tumor or aneurysm?
Seizures?
Brain Injury?

- (If yes) When was the last time you were affected by that condition?

Do you currently have or have a history of any of the following conditions or diseases? Please listen to the entire list of conditions or diseases before answering YES or NO.

Heart Attack?
Angina (chest discomfort/pain/pressure upon physical exertion)?
Congestive heart failure?
Cardiomyopathy?

Heart angioplasty, stent or bypass surgery?
Heart valve surgery/replacement or valve disease (e.g., aortic stenosis, mitral stenosis or regurgitation)?
Pacemaker or implantable defibrillator?
Peripheral artery or vascular disease in legs?
Atrial fibrillation or flutter?

(If yes) When was the last time you were affected by that condition?

Are you currently using investigational or study medical device or drug or have you in the last 3 months?

Do you currently consume more than 9 alcoholic drinks a week?

Have you been on any hormone replacement therapy within the past 3 months?

Has your doctor ever said that you have a heart condition and that you should do physical activity recommended by a doctor?

Do you feel pain in your chest when you do physical activity?

In the past month, have you had chest pain when you were not doing physical activity?

Do you lose your balance because of dizziness, or do you ever lose consciousness?

Do you have a bone or joint problem that could be made worse by a change in your physical activity?

Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?

Do you have any absolute contraindications to exercise (i.e., acute myocardial infarction, severe orthopedic or musculoskeletal limitations)?

Do you have a history of chest pain, shortness of breath, or fainting?

Do you have physical disability that would limit range of motion through exercises such as sitting, standing and inability to walk one block?

Do you know of any other reason why you should not do physical activity?

Do you have any plans to move from the area in the next three months?

Are you comfortable using Zoom or video communication for your sessions?
(If no) Are you willing to learn how to use Zoom?

Type of Clinical Trial:

- **X** Investigator-initiated (UI/HCCC)
- **X** Pilot study
- ❑ Phase I/II
- ❑ Phase III
- ❑ Interventional Treatment
- ❑ Non-Interventional
- ❑ Investigator-initiated, participating site
- ❑ Phase I
- ❑ Phase II
- ❑ Compassionate use
- **X** Interventional Non-Treatment

Study risk-level:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- **X** Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ❑ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

***** *Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator-initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Register all subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations
- Provide an annual progress report to the DSMC via OnCore data export

Selected monitoring strategy based on risk-level:

Risk Level 2

Interventional trials with a risk of death* (<1% or any adverse event 1% – 5%), e.g. behavioral interventions, nutritional therapies, low risk procedures (e.g., endoscopy, glucose-tolerance tests, induced sputum, skin or muscle biopsy, nasal wash, lumbar puncture, bone marrow biopsy, imaging requiring sedation), as well as therapeutic trials involving agents with known safety profiles already licensed for the indication and age group. Most disease-prevention trials will be considered at least a Risk Level 2.

Study Safety Review

The PI or designated study personnel will review all study data for completeness

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation must begin from the first day of study intervention and typically continue through the 30-day follow-up period after the intervention is discontinued.

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade (according to NCI's Common Toxicity Criteria (CTCAE)), onset and resolved dates (if applicable), and the relationship to the study drug should be included. Documentation should occur in real time. The principal investigator has final responsibility for determining the attribution of the event as it is related to the study drug.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event must begin after signing of the informed consent and continue through the 30-day follow-up period after treatment is discontinued.

Investigators must report to the DSMC any serious adverse events (SAE), whether they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 24 hours of learning of the event.

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

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Data Monitoring and Management

Subject Registration

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Each subject registration includes the following:

- The subject's IRB approved (version date) consent form and the date of their consent.
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

All subject registration information is expected to be entered into OnCore within **2 (two) business days** after the subject's study visit.

Subject Data

For HCCC investigator-initiated trials, research staff are responsible for entering subject study data (data collection) into OnCore electronic case report forms (eCRFs). These eCRFs must be approved by the PI and statistician prior to study activation to ensure sufficient and necessary data acquisition. All information entered into eCRFs will be traceable to the source documents which are generally maintained in the subject's file.

eCRF data entry needs to be timely and should be entered into OnCore as soon as possible but no later than **14 (fourteen) business days** after the subject's visit, including adverse events, tumor measurements, administration of study medication, concomitant medications, labs, and vitals. Physical exam assessments must be entered no later than **14 (fourteen) business days** following completion of the physician's clinic note in the medical record.

Timely data entry facilitates remote monitoring of data, allows the data to progress appropriately through the data cleaning process, and helps prevent a backlog of data queries.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all data are entered completely, accurately, and within time requirements outlined above. The assigned DSMC monitor will coordinate and complete the data monitoring review. When the time comes to monitor a study (based on patient accrual and assigned risk level of trial) the monitor arranges for a selection of cases to be reviewed from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries via OnCore (linked to the eCRF) to resolve missing, incomplete, and/or incorrect information. A member of the research

team is expected to respond to these monitoring queries within **14 (fourteen) business days.**

The monitoring process can often identify misunderstandings or deficiencies in the written, research protocol requirements earlier in the study process and thereby improve data quality and reduce rework.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

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