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Title of Protocol:
The Effects of Moderate Exercise on Distress, Quality of Life, and Biomarkers of Angiogenesis and Chronic Stress in Ovarian Cancer Survivors – a Randomized Controlled Trial

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PROTOCOL SYNOPSIS

Protocol Title	*The Effects of Moderate Exercise on Distress, Quality of Life, and Biomarkers of Angiogenesis and Chronic Stress in Ovarian Cancer Survivors*
Protocol Number	*10045*
Protocol Sponsor	*NCI*
Trial Phase	*N/A*
Trial Type	*Randomized Controlled Trial*
Clinical Indication	*Ovarian, Fallopian Tube, and Peritoneal Cancer*
Study Objectives	*1. To test the effects of the moderate exercise intervention versus controls on psychosocial distress levels, assessed by the Perceived Stress Scale and the Hospital Anxiety and Depression Scale anxiety and depression subscales.* *2. To test the effects of the moderate exercise intervention versus controls on Quality of Life, assessed by the 36-item Short Form Health Survey - physical component score for Quality of Life,).* *2. To test the effects of the moderate exercise intervention versus controls on serum levels of IL-6 and VEGF (biomarkers of angiogenesis).* *3. To test the effects of the moderate exercise intervention versus controls on levels of evening salivary cortisol and urinary norepinephrine, biomarkers of chronic stress.*
Study Design	*Individuals with stage II-IV ovarian cancer (N=98) who have completed primary treatment within one to six months and are in clinical remission will be randomized in a 1:1 ratio to a 24-week home-based exercise program or wait-list control. The exercise prescription will consist of 150 minutes of moderate aerobic exercise (the equivalent of brisk walking or higher intensity) per week, with weekly telephone-based support by an exercise physiologist. The control group will perform their usual activities and will be offered the exercise intervention after 24 weeks. Baseline and 24-week assessments will include validated questionnaires assessing distress and health-related quality of life, serum levels of IL-6 and VEGF, salivary cortisol levels measured at bedtime for three consecutive days, and 24-hour urinary norepinephrine levels. Participants will also complete questionnaires at 12 weeks to provide additional longitudinal data. Adherence to the intervention will be assessed by daily activity logs, actigraphs, and completion of weekly telephone calls.*
Population	*Individuals (age 18 and over) with stage II-IV ovarian, fallopian tube, or peritoneal carcinoma (collectively referred to as ovarian cancer) who have completed primary surgery and chemotherapy within one to six months and are in clinical remission.*
Primary Endpoints	*1. Distress – mean change from baseline to 24 weeks between the exercise intervention and control group in the Perceived Stress Scale, and in the Hospital Anxiety and Depression Scale anxiety and depression subscales.* *2. Quality of Life – mean change from baseline to 24 weeks between the exercise intervention and control groups in the 36-item Short Form Health Survey - Physical Component Score.* *3. Biomarkers of angiogenesis - mean change from baseline to 24 weeks between the exercise intervention and control group in mean levels of IL-6, VEGF.* *4. Nocturnal cortisol (biomarker of chronic stress) – mean change from baseline to 24 weeks between the exercise intervention and control group in mean evening salivary cortisol level.*

Exploratory Endpoints	*1. Urinary norepinephrine (biomarker of chronic stress) - mean change from baseline to 24 weeks between the exercise intervention and control group in mean 24-hour urine norepinephrine level.* *2. Mean change in outcomes (distress, Quality of Life, biomarkers) by category of exercise adherence (Mean change in outcomes (distress, Quality of Life, biomarkers) by category of exercise adherence (Percent of participants who exercised: ≥150 minute per week (≥100% of goal), 120-149 minutes per week, (≥80% of goal), 90-119 minutes per week (≥60% to <80% of goal), 60-89 minutes per week (≥40% to <60% of goal), 30-59 minutes per week (≥20% to <40% of goal), <30 minutes per week (<20% of goal)).* *3. Correlations of levels of distress or Quality of Life with changes in biomarkers*
Type of control	*Waitlist exercise intervention*
Investigation Drug	*N/A*
Dose	*N/A*
Route of administration	*N/A*
Regimen	*N/A*
Trial Blinding	*N/A*
Treatment Groups	*Home-based exercise intervention*
Treatment Schedule	*The exercise prescription will consist of 150 minutes of moderate aerobic exercise (the equivalent of brisk walking or higher intensity) per week, with weekly telephone-based support by an exercise physiologist. The control group will maintain habitual levels of physical activity and will be offered the exercise intervention after 24 weeks.* *Baseline and 24-week assessments will include validated questionnaires assessing distress and health-related quality of life, serum levels of IL-6 and VEGF, salivary cortisol levels measured at bedtime for three consecutive days, and 24-hour urinary norepinephrine levels. Participants will also complete questionnaires at 12 weeks to provide additional longitudinal data.* *Adherence to the intervention will be assessed by daily activity logs, actigraphs, and completion of weekly telephone calls.*
Efficacy Assessments	*Less psychosocial distress, improved quality of life, decreased biomarkers of angiogenesis and chronic stress hypothesized in the exercise arm group.*
Number of trial subjects	*98*
Estimated duration of trial	*2 years*
Duration of Participation	*24 weeks*

ABBREVIATIONS

AE	Adverse event
CRF	Case report form
CTCAE	NCI Common Terminology Criteria for Adverse Events
GEE	generalized estimating equations
IL-6	Interleukin-6
MAR	mechanism is at random
NCTN/NCORP	National Clinical Trials Network/NCI Community Oncology Research Program
NIM	nonignorable missing
PATS	Protocol Accrual Tracking System
SAE	Serious adverse event
VEGF	Vascular endothelial growth factor

Table of Contents

1.0 GENERAL INFORMATION

This randomized controlled trial will investigate the effects of exercise on psychological distress, quality of life, and biomarkers associated with poor prognosis in individuals with ovarian cancer. The study results will help us to better understand the biological pathways through which exercise may improve cancer survival. The majority of individuals with ovarian cancer experience poor quality of life and ultimately die of their disease despite conventional therapy; determining if exercise can improve distress, quality of life, and biomarkers of prognosis would be a major advance for individuals with ovarian cancer. The study will be conducted in compliance with the IRB approved protocol, associated Federal regulations and all applicable IRB requirements.

1.1 Protocol Title: The Effects of Moderate Exercise on Distress, Quality of Life, and Biomarkers of Angiogenesis and Chronic Stress in Ovarian Cancer Survivors – a Randomized Controlled Trial

1.2 Sponsor Information: National Cancer Institute

1.3 Investigator Information:

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2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

The majority of people with ovarian cancer present with advanced-stage disease (1). Although individuals usually achieve initial remission, most experience recurrence and die of chemoresistant disease, with a five-year survival rate of 27% (1). Ovarian cancer and its treatments are associated with a variety of persistent negative side effects including depression, anxiety, fatigue, and reduced quality of life (2-5). Physical activity may help cancer survivors reduce distress, improve quality of life, and possibly improve survival.

Two observational studies suggest that physical activity is associated with better quality of life in ovarian cancer survivors (6, 7), which is important because ovarian cancer survivors have persistently reduced quality of life even after treatment is completed (2-4). However, only 31% of ovarian cancer survivors achieve public health guidelines for physical activity (7). A Cochrane review of randomized controlled trials in cancer survivors (multiple cancer types) found that short-term exercise improved physical functioning, cancer-related fatigue, and quality of life (8). The effectiveness of exercise training is especially well studied in breast cancer survivors (9, 10). Whereas most people with breast cancer are diagnosed with early-stage disease, the majority of individuals with ovarian cancer are diagnosed at advanced-stage, undergo intensive chemotherapy, and have worse quality of life. The efficacy of exercise is understudied in ovarian cancer, and our study is significant because identifying interventions that can benefit ovarian cancer patients is an unmet need.

Most exercise trials in cancer survivors have been carried out either during chemotherapy or more than one year after completing primary treatment (8). However, patients may be most likely to benefit from an exercise intervention in the early survivorship period. Individuals with ovarian cancer have significantly reduced physical functioning and quality of life immediately after completing chemotherapy (11) and experience significant psychosocial distress (2-4). The early survivorship period is an optimal time point to commence an exercise program that addresses the decreased physical fitness caused by cancer treatment, as well as treatment-related side effects such as fatigue (12, 13). Aiming to increase physical activity during this period may capitalize on the "teachable moment," as cancer survivors are more likely to make lifestyle changes when in closer proximity to their cancer diagnosis (14, 15). In addition, the majority of ovarian cancer survivors prefer to start an exercise program either immediately after or within three to six months of treatment (16). Our study will enroll individuals with ovarian cancer who have completed chemotherapy within one to six months and will be the first study to evaluate the effects of exercise in ovarian cancer survivors during the early survivorship period.

In our proposed two-arm RCT, we will assess the impact of a six-month moderate exercise program in ovarian cancer survivors who have recently completed primary treatment, compared to controls on levels of psychosocial distress and quality of life, and on biomarkers associated with poor prognosis in ovarian cancer. A home-based intervention will be implemented because ovarian cancer survivors have previously reported a preference for home-based exercise (16). Individuals randomized to the intervention will receive one in-person baseline training session and weekly telephone consultations from our exercise physiologist, with personalized, clear instructions on how to gradually and safely attain a goal of 150 minutes of moderate-intensity physical activity per week. We have recently demonstrated in a large randomized controlled trial that a home-based exercise intervention is feasible in ovarian cancer survivors with excellent adherence rates (PI: Irwin) (17). Our home-based exercise program with behavioral support, initiated within one to six months of completion of chemotherapy, may help ovarian cancer survivors to initiate exercise, accelerate fitness, and improve distress and treatment-related symptoms. Compared to a supervised exercise program, a home-based program is more generalizable, increases patient access, and will be easier to implement in subsequent randomized controlled trials. Thus, the results of our study will guide future trial design, clinical practice, and survivorship planning.

Observational studies suggest an association between physical activity and improved survival in multiple cancer types (18-20). An analysis of the Women's Health Initiative evaluated the association between physical activity at the time of study enrollment (mean seven years prior to ovarian cancer diagnosis) and ovarian cancer survival (N=600). Individuals who engaged in any vigorous-intensity exercise (≥7 metabolic equivalents) at baseline had a 26% lower risk of cancer-specific mortality, compared to those performing moderate and/or no exercise; individuals in the moderate intensity category had a non-statistically significant trend towards a 32% reduced risk of dying from the disease (21). Although suggestive of a survival benefit to physical activity, this study examined physical activity years prior to ovarian cancer diagnosis and was not a randomized study, so causality cannot be assumed.

The biobehavioral mechanisms through which physical activity may decrease mortality in cancer survivors are unknown. We will investigate the potential role of exercise in reversing biologically harmful effects of psychological distress. Psychological distress is common in ovarian cancer survivors (2-5), and chronic stress/distress may promote cancer growth through prolonged activation of the Hypothalamic Pituitary Adrenal axis and of the sympathetic nervous system, resulting in excess secretion of cortisol and norepinephrine, respectively (22-24). This in turn alters expression of cytokines such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), which are involved in angiogenesis and tumor invasion (25-27). Cortisol also has direct effects on tumor growth (28, 29). Psychological distress, depression, and poor social support are associated with elevated serum IL-6, VEGF, evening salivary cortisol, and elevated tumor norepinephrine levels in ovarian cancer survivors (30-34). Elevated IL-6, VEGF, and salivary evening cortisol all predict worse survival in ovarian cancer patients (N=90 to 314) (35-38). Increased *ADRB2* gene expression is also associated with decreased ovarian cancer survival (39), and non-selective beta-blocker use is associated with improved survival (40, 41). Studies using animal models of breast and prostate cancer suggest that exercise may decrease tumor growth (42-44), modulate expression of prometastatic genes with a shift towards reduced metastasis (45), and decrease IL-6 and VEGF (42, 44, 45). Limited clinical studies also suggest exercise decreases VEGF, IL-6, and improves diurnal cortisol in cancer survivors (46-48). Combined exercise and diet interventions in persons without cancer have also been shown to decrease serum IL-6 (49-51). Exercise decreases serum norepinephrine in women with fibromyalgia (52).

The data from this R21 project will justify a larger randomized controlled trial of a moderate exercise intervention in OC survivors that will be powered to detect a difference in progression-free survival and further elucidate biobehavioral pathways through which physical activity may affect cancer prognosis and survival. This study would significantly differ from the NCTN/NCORP randomized controlled trial that is testing diet, weight maintenance, and low-level physical activity on quality of life and progression-free survival (53). As some randomized controlled trials have suggested that moderate activity is more important than low-level activity (8), our study provides additional value. The majority of individuals with ovarian cancer experience poor quality of life (4) and ultimately die of their disease despite conventional therapy. Determining if exercise can improve quality of life and survival would have a significant impact on people with ovarian cancer.

2.2 Preclinical Data

Not applicable

2.3 Clinical Data to Date

We have the necessary expertise to conduct the proposed study and have been involved in numerous clinical trials of exercise interventions. We have strong experience in conducting behavior change interventions in postmenopausal women and have demonstrated the ability to recruit and retain women in complex long-term intervention studies. Dr. McTiernan's clinical trials of facility-based and home-based exercise have demonstrated excellent adherence and retention rates. Many of the staff from these successful prior studies are involved with our proposed R21 study. Examples: 1) the Physical Activity for Total Health trial (54-56) tested the effects of exercise on endogenous sex hormones in overweight postmenopausal women (N=173). It randomized women to moderate-intensity aerobic exercise (both facility and home-based) or stretching control, with only six intervention dropouts. On average, the exercisers participated in moderate-intensity exercise for 199 ± 82 min/week. 87% adhered to 150 min/week. Exercise participants experienced a 13% increase in fitness (VO_2 max) versus 1% in stretching controls ($p < 0.001$). 2) A pilot study of an exercise and diet intervention for ten breast cancer survivors (57) provided information on the feasibility of recruiting, enrolling, and maintaining an eight-week supervised moderate-intensity exercise program for persons with cancer. Nine individuals completed the entire exercise program and completed 22.1 of the 24 sessions. Significant changes in weight and body fat mass were achieved, pointing to the investigators' success in working with high-risk patients in an exercise-diet program. 3) Large randomized controlled trials testing the effects of exercise with and without diet include the NEW study (N=439 postmenopausal women) (58-65) and the APPEAL study (N=202 men and women), (66-74) demonstrating our success in year-long interventions and biomarker assessments.

We (PI: Dr. Irwin) recently completed a randomized controlled trial of 144 physically inactive ovarian cancer survivors, randomized to six months of home-based, moderate-intensity exercise vs. control (17). At baseline, participants were on average 1.7 years post-diagnosis and exercised 31 minutes per week; 55% had advanced stage (III-IV). Intervention arm participants exercised a mean of 166 minutes per week of moderate exercise; 65% reported adhering to the goal of ≥150 minutes per week, and 84% reported ≥120 minutes per week (80% of goal). 83% of participants with stage III-IV ovarian cancer exercised at least 80% of goal, compared to 75% of participants with stage I-II ($p=0.41$), demonstrating that individuals with advanced-stage ovarian cancer can also exercise. Ovarian cancer survivors are highly motivated to adhere

to an exercise program and can exercise at recommended levels. Individuals in the exercise arm improved physical health-related quality of life, compared to a decreased physical health-related quality of life in control arm (mean 36-item Short Form Health Survey- Physical Component Score change of 1.8 ± 1.1 vs. -2.0 ± 1.2, *P* = 0.02). A weakness of this study is that it relied on self-report for exercise adherence. We include actigraphy as an objective measure in our proposed study.

2.4 Study Agent
Not Applicable

2.5 Dose Rationale
Not Applicable

2.6 Other Agents
Not Applicable

2.7 Risks/Benefits
Our proposed study will be the first randomized trial of moderate exercise in ovarian cancer survivors during the early survivorship period to test its effects on psychosocial distress, quality of life, biomarkers of angiogenesis, and on biomarkers of chronic stress (evening cortisol and urinary norepinephrine). The study results will help us to better understand the biological pathways through which exercise may improve cancer survival. The majority of individuals with ovarian cancer experience poor quality of life and ultimately die of their disease despite conventional therapy; determining if exercise can improve distress, quality of life, and biomarkers of prognosis would have a major impact on women with ovarian cancer.

The participants will benefit from the knowledge to be gained about their own health and will benefit from their increased fitness. We believe that the risks associated with participation in this study are small and are greatly outweighed by the potential benefits of the interventions. The study will contribute to our understanding of the role that exercise may play in reducing distress, increasing quality of life, and improving biomarkers of prognosis in ovarian cancer.

Potential risks include:

- Questionnaires and weight measurements: Collection of demographic and other information via questionnaires may be embarrassing to some individuals. Weight measurement or anthropometric measurement may be embarrassing to some individuals.
- Blood draws: There is a small risk of light-headedness, bleeding, or discomfort/bruising at the site of the blood collected.
- Exercise training: The major risks include fatigue and muscle soreness, and possibly joint or skeletal injury. These risks are reduced by proper warm-up/cool down periods, conservative and individual exercise prescriptions and progression, and careful education about ways to reduce injury by an experienced exercise physiologist. The likelihood of a myocardial infarction or sudden cardiac event is extremely low – there is a <0.1% chance of a myocardial infarction and <0.02% chance of sudden death in a population at high risk for cardiovascular disease during a maximal treadmill protocol; the risks in this study will be considerably less, because we are screening participants so that only women without known or suspected coronary disease, and without contraindications to exercise testing and initiating an exercise program will be eligible to participate. Furthermore, the intervention will not include the type of vigorous activity required in a maximal treadmill test. In addition, participants will be performing exercise at moderate intensity, and not at maximal effort, and will be performing exercises of their own choosing (under close guidance by the exercise physiologist).
- Measurement of physical activity by activity monitor: Some people may find it inconvenient or embarrassing to wear the monitor.
- Inadvertent disclosure of confidential medical information and individual results.

3.0 OVERVIEW OF CLINICAL TRIAL

3.1 Study Objectives

3.1.1 Primary Objectives

1. To test the effects of the moderate exercise intervention versus controls on psychosocial distress levels, assessed by the Perceived Stress Scale and the Hospital Anxiety and Depression Scale anxiety and depression subscales
2. To test the effects of the moderate exercise intervention versus controls on Quality of Life, assessed by the 36-item Short Form Health Survey - Physical Component Score.
3. To test the effects of the moderate exercise intervention versus controls on serum levels of IL-6 and VEGF (biomarkers of angiogenesis).
4. To test the effects of the moderate exercise intervention versus controls on levels of evening salivary cortisol (a biomarker of chronic stress).

3.1.2 Exploratory Objectives

1. To evaluate the effects of the moderate exercise intervention versus controls on 24-hour urinary norepinephrine levels (a biomarker of chronic stress).
2. To determine if improvements in levels of distress or Quality of Life correlate with changes in biomarkers.
3. To evaluate for a dose-response relationship between exercise and our outcomes of interest.

3.1.3 Safety Objectives

1. To evaluate the safety of the moderate exercise intervention.

3.2 Study Population

Individuals with histologically or cytologically confirmed stage II-IV epithelial ovarian, peritoneal, or fallopian tube carcinoma (collectively referred to as ovarian cancer) who have completed primary surgery and chemotherapy within one to six months of screening, and are in clinical remission (no clinical evidence of disease on exam and normal CA-125 level) will be eligible. Individuals must be physically able to undertake a moderate exercise program. Individuals will be excluded if they have contraindications to initiating a training program (75), or if they already exercise >90 minutes per week of moderate intensity. Persons with peripheral neuropathy and lower extremity edema will not be excluded, but will be evaluated by their oncologist and the exercise physiologist for safety.

3.3 Study Design

Individuals with stage II-IV ovarian cancer (N=98) who have completed primary treatment within one to six months and are in clinical remission will be randomized in a 1:1 ratio to a 24-week home-based exercise program or wait-list control. The exercise prescription will consist of 150 minutes of moderate aerobic exercise (the equivalent of brisk walking or higher intensity) per week, with weekly telephone-based support by an exercise physiologist. The control group will perform their usual activities and will be offered the exercise intervention after 24 weeks. Baseline and 24-week assessments will include validated questionnaires assessing distress and health-related quality of life, serum levels of IL-6 and VEGF, salivary cortisol levels measured at bedtime for three consecutive days, and 24-hour urinary norepinephrine levels. Participants will also complete questionnaires at 12 weeks to provide additional longitudinal data. Adherence to the intervention will be assessed by daily activity logs, actigraphs, and completion of weekly telephone calls.

3.3.1 Primary Endpoints

1. Distress – mean change from baseline to 24 weeks between the exercise intervention and control group in the Perceived Stress Scale, and in the Hospital Anxiety and Depression Scale anxiety and depression subscales.
2. Quality of Life – mean change from baseline to 24 weeks between the exercise intervention and control groups in the 36-item Short Form Health Survey - Physical Component Score.
3. Biomarkers of angiogenesis- mean change from baseline to 24 weeks between the exercise intervention and control group in mean levels of IL-6, VEGF.
4. Nocturnal cortisol (biomarker of chronic stress) – mean change from baseline to 24 weeks between the exercise intervention and control group in mean evening cortisol level.

3.3.2 Exploratory Endpoints

1. Urinary norepinephrine- mean change from baseline to 24 weeks between the exercise intervention and control group in mean 24-hour urine norepinephrine level.
2. Mean change in outcomes (distress, Quality of Life, biomarkers) by category of exercise adherence (Percent of participants who exercised: ≥150 minute per week (≥100% of goal), 120-149 minutes per week, (≥80% of goal), 90-119 minutes per week (≥60% to <80% of goal), 60-89 minutes per week (≥40% to <60% of goal), 30-59 minutes per week (≥20% to <40% of goal), <30 minutes per week (<20% of goal).
3. Correlations of levels of distress or Quality of Life with changes in biomarkers

3.3.3 Safety Endpoints

1. Serious adverse events and total adverse events attributable to the exercise intervention will be reported.

3.4 Estimated Accrual: 98 participants

3.5 Name of Sponsor/Funding Source: National Cancer Institute

4.0 SAFETY CONSIDERATIONS

4.1 Stopping Rules

N/A – the risk of serious adverse events with moderate exercise is very low. There is a <0.1% chance of a myocardial infarction and <0.02% chance of sudden death in a population at high risk for cardiovascular disease during a maximal treadmill protocol; the risks in this study will be considerably less, because we are screening participants so that only those without contraindications to exercise testing and initiating an exercise program will be eligible to participate. In addition, participants will be performing exercise at moderate intensity, and not at maximal effort, and will be performing exercises of their own choosing (under close guidance by the exercise physiologist).

4.2 Safety Measures

Individuals will be instructed to stop exercise and contact their doctor if they have any of the following symptoms during exercise or after an exercise session:
– Disorientation, dizziness, blurred vision or fainting
– Sudden onset of nausea, vomiting
– Unusual or sudden shortness of breath
– Irregular heartbeat, palpitations, chest pain
– Leg/calf pain, bone pain, unusual joint pain or pain not caused by injury
– Muscle cramps or sudden onset of muscular weakness or fatigue

The most common risks of exercise include fatigue and muscle soreness, and possibly joint or skeletal injury. These risks are reduced by proper warm-up/cool down periods, conservative and individual exercise prescriptions and progression, and careful education about ways to reduce injury by an experienced exercise physiologist. Musculoskeletal injuries will be assessed by one of the study clinicians. Individuals with a suspected serious musculoskeletal injury as a result of exercise will be instructed to be evaluated by their personal physician or to be evaluated at urgent care or the emergency department. Subsequent exercise will either be held to allow for recovery, or modified, depending on the nature of the injury and physician assessment. If a medical issue develops which is not related to exercise, the exercise prescription will also be modified as needed.

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria

5.1.1 Histologically or cytologically confirmed stage II-IV primary epithelial ovarian, fallopian tube, or peritoneal cancer. If site of origin cannot be specified, carcinoma of Mullerian origin may be included if most consistent with ovarian/fallopian tube/peritoneal origin rather than uterine origin. The following histologic epithelial cell types are eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, clear cell carcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's tumor, undifferentiated carcinoma, carcinosarcoma, or adenocarcinoma not otherwise specified. Individuals with neoplasms of low malignant potential (borderline tumors) are not eligible.

5.1.2 Subjects must have no evidence of disease, as defined by their treating oncologist, and with normal CA-125 (≤35).

5.1.3 Subjects must have completed primary surgery and adjuvant chemotherapy for treatment of ovarian, fallopian tube, of peritoneal cancer within one to six months of screening. Maintenance therapy will be allowed as long as the participant is in clinical remission– including hormonal agents, anti-angiogenesis agents, PARP inhibitors, and immunotherapy. Prior radiation therapy is allowed, as long as it has been completed within one to six months of screening. Subjects may have received prior therapies (including surgery, chemotherapy, radiation therapy) for other malignancies in the past.

5.1.4 Subjects must be 18 or older.

5.1.5 ECOG status of 0, 1, or 2. See Appendix B.

5.1.6 Pregnancy and the need for contraception:
N/A – participants with ovarian cancer have undergone hysterectomy with removal of ovaries and tubes as part of surgical treatment, and therefore do not have the potential to become pregnant.

5.1.7 Ambulatory

5.1.8 Ability to understand and the willingness to sign a written informed consent document.

5.1.9 Individuals participating in most other clinical trials are eligible provided their enrollment in the other trial does not impair their ability to participate in the physical activity interventions and study assessments required in this trial. The other clinical trial must not be a behavioral intervention trial.

5.2 Exclusion Criteria

5.2.1 Subjects who have had primary surgery, chemotherapy and/or radiation therapy within 4 weeks prior to screening. Subjects may have received other surgeries not performed for primary treatment (for example, removal of intraperitoneal port, laparoscopic cholecystectomy, etc.) within 1 month of screening as long as they do not have post-operative restrictions that would preclude participating in a moderate intensity exercise program once enrolled in the clinical trial.

5.2.2 Self-reported inability to walk at least 2 blocks (at any pace).

5.2.3 Prior brain metastasis is not an exclusion, as long as subject is in clinical remission.

5.2.4 Uncontrolled or concurrent illness including, but not limited to: unstable angina pectoris, recent (within six months) myocardial infarction, uncontrolled cardiac arrhythmia, uncontrolled congestive heart failure, hypertrophic obstructive cardiomyopathy, uncontrolled hypertension (systolic > 200, diastolic > 120), conditions (cardiovascular, respiratory, or musculoskeletal disease or joint problems) that preclude moderate physical activity. Subjects with a history of cardiac arrest, or those with moderate/severe aortic or mitral stenosis may be eligible if their treating physician determines that moderate physical activity is safe. Moderate arthritis that does not preclude physical activity is not a reason for ineligibility. Individuals with lymphedema or peripheral neuropathy will not be excluded. They will be evaluated by the exercise physiologist for safety and modifications to the exercise prescription will be made as appropriate.

5.2.5 Psychiatric illness/social situations that would limit compliance with study requirements.

5.2.6 Already physically active >90 minutes per week of moderate exercise.

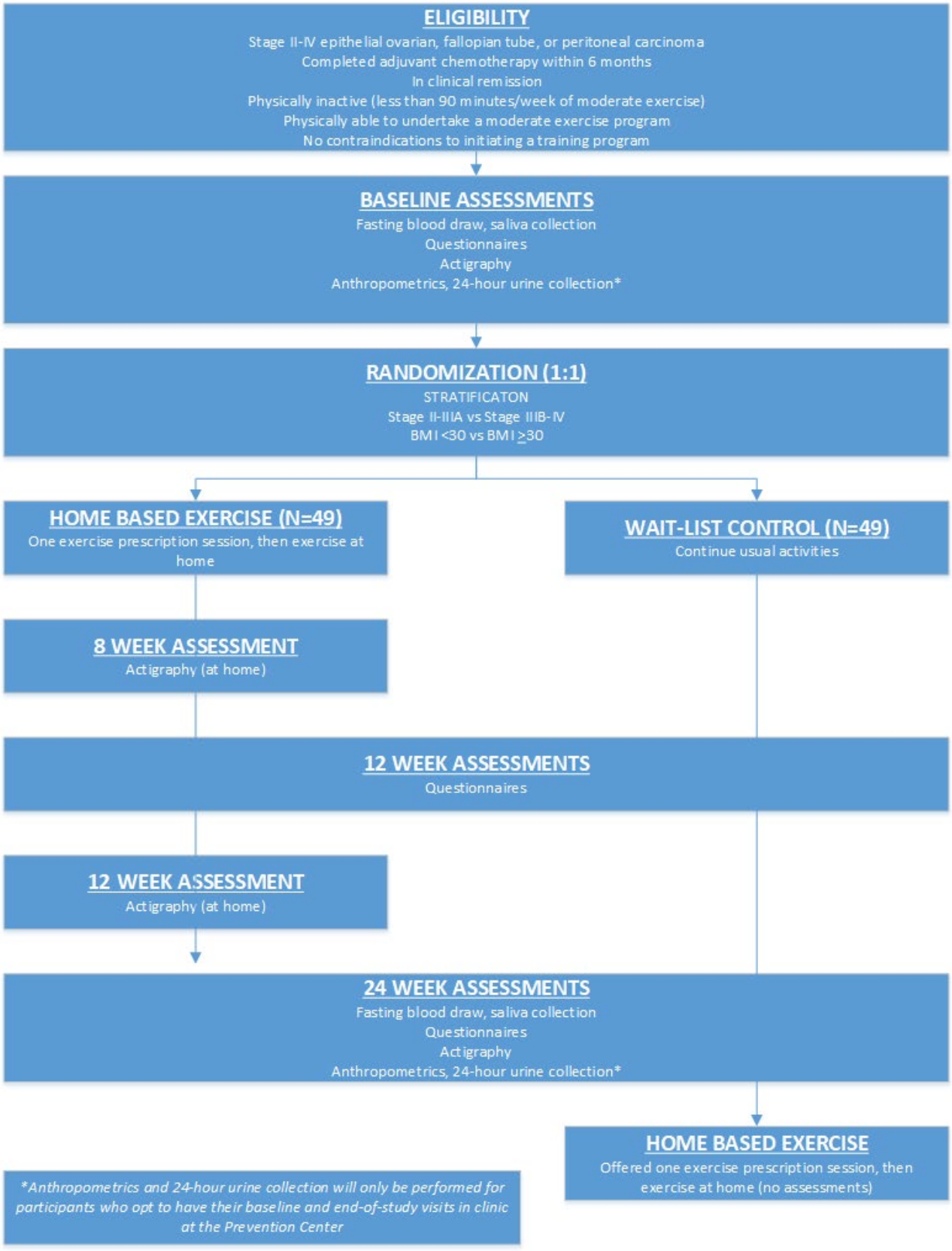
6.0 SUBJECT REGISTRATION

Subjects will be registered by the Fred Hutch/UW Study Coordinator and entered into the Protocol Accrual Tracking System (PATS). A complete, signed, study consent and HIPAA consent are required for registration.

7.0 TREATMENT PLAN

7.1 Treatment Plan Overview

SCHEMA



7.2 Administration of IP or Placebo

Home-based Exercise Intervention Arm: Participants will meet with the exercise physiologist at the Prevention Center for a 60 minute one-on-one session. Participants who are not willing or able to go to the Prevention Center for an in-person session may have this session conducted through Telehealth (HIPAA-compliant videoconferencing). They will receive an individualized exercise prescription with an ultimate goal of moderate aerobic exercise for 150 minutes per week. Exercise prescriptions will be modified as appropriate for those with neuropathy, lower extremity edema, or other physical limitations or medical conditions (76, 77). Various exercises such as brisk walking, aerobics, and cycling will be suggested, with instruction on proper exercise techniques and safety (such as warm-up or stretching). Slow implementation of the exercise goals will reduce chances of injury and increase participant adherence and sense of accomplishment. The session length and exercise intensity will gradually increase over the first eight weeks to the ultimate goal and will be maintained for the rest of the study period. Participants will learn to determine exercise intensity levels using the Borg rating of perceived exertion scale, a validated tool for monitoring and prescribing exercise intensity that correlates well with heart rate (78). After each exercise session, participants will log their duration, perceived intensity, and exercise activity. They may complete their exercise log on paper or electronically. Participants opting to complete the daily exercise logs on paper rather than electronically will be asked to mail their exercise logs in weekly in a study-provided stamped addressed envelope. If they prefer, they may also photograph the week's exercise log and email or text it to the study coordinator.

A sample progression of exercise goals is provided below, but the specific exercise prescription will be individualized by the exercise physiologist based on participant's initial level of fitness and physical functioning, as well as progress made throughout the study.

Week #	Total # of Exercise Sessions Per Week	Minutes of Aerobic Exercise Per Session	Total Minutes Per Week	Rate of Perceived Exertion (RPE, Borg 6-20 scale)
1	3	15	45	9-11
2	3	20	60	9-11
3	3	25	75	9-11
4	3	30	90	10-12
5	4	30	120	10-12
6	4	30	120	11-13
7	4	30	120	11-13
8-24	5	30	150	12-14

Behavioral support: The exercise physiologist will contact participants weekly by phone. The purpose of the phone calls will be to provide motivational support, troubleshoot barriers to exercise, and to adjust training intensity and progression throughout the intervention. The exercise physiologist will ask participants whether they experienced any excessive fatigue, muscle soreness, injury, or other symptoms during the past week. During each phone call, the exercise physiologist will provide assistance with overcoming barriers to exercise, provide an update exercise prescription for the upcoming week, and encourage flexibility/stretching exercises. Although weekly phone calls are preferred, the exercise physiologist may reach out to the participant via email (if the participant agrees) to discuss progress over the past week if the exercise physiologist and participant are unable to schedule a mutually agreeable time for a phone conversation. Participants will also have the opportunity to contact the physiologist via email if they desire.

Participants will receive written materials on exercise techniques and motivational strategies, as well as general information about ovarian cancer and survivorship. Participants will be logging their exercise daily, and they may view/track their weekly progress (self-monitoring). If participants if have not completed their exercise log for more than a week, they will be reminded to complete them by the exercise physiologist during their weekly telephone call or will receive a reminder by the study coordinator. "Badges" will be awarded electronically for accomplishments such as meeting 75% or 100% of a weekly exercise goal. Badges will be built into REDCap and appear at the end of the week once a participant has entered their exercise log data. Participants may opt out of any portion of this e-technology at any time. Participants who choose to fill out the exercise logs on paper rather than electronically will be asked to mail each week's completed exercise log back in a self-addressed stamped envelope provided by the study coordinator after she has spoken with the exercise physiologist during her weekly telephone call. If participants prefer, they may also photograph the week's exercise log and email or text it to the study coordinator.

Wait-list Control Arm: Participants will continue their usual activities. They will be offered the same home-based exercise intervention (with behavioral support), after completing their 24 week assessments. At the start of the study, participants in the control arm will receive general education materials about ovarian cancer and survivorship. After 24 weeks, they will be given the written materials on exercise techniques and motivational strategies, and offered the exercise intervention.

7.3 Concomitant Medication and Supportive Care Guidelines

All participants on either arm of the study may receive any care deemed beneficial by themselves or their treating physicians. They may take any medications or treatments indicated for concomitant medical conditions. Participants experiencing muscle soreness or discomfort as a result of exercising may take supportive over-the-counter medications including acetaminophen, non-steroidal anti-inflammatory drugs, and other analgesics (as long as they have not been instructed by their doctor to avoid those medications due to medical contraindications) or any medications prescribed by their physician. They may also apply ice or heat for symptomatic relief. In the event of a suspected injury, participants will be instructed to seek medical evaluation and treatment as indicated.

7.4 Duration of Therapy

After baseline assessments (done at FHCRC Prevention clinic or home-based, see section 8.1) and randomization, participants randomized to the exercise arm will receive a one-on-one session with the exercise physiologist for one hour either at the FHCRC Prevention Center or through Telehealth. The exercise intervention will last for 24 weeks. During the intervention, they will not have any clinic visits. They will receive weekly telephone calls for support. All assessments during the intervention (actigraphy, surveys) will be completed at home. At the end of the study, all participants (exercise intervention arm and wait-list control arm) will complete end-of-study assessments either at clinic, or home-based (see section 8.1). After 24 weeks, participants in the wait-list control arm will be offered the home-based exercise intervention, which would also last for 24 weeks. Participants receiving the delayed intervention will be offered the single one-on-one session with the exercise physiologist and receive weekly telephone calls for support, but will not have any additional clinic visits or any assessments during or after the delayed intervention. Participants who were enrolled but ultimately became ineligible by falling significantly outside of the eligibility window (within 6 months of completing chemotherapy) before the baseline visit could occur due to COVID-19 related delays in visit scheduling. They may receive the exercise program without any data collection activities if they has a strong interest. We anticipate this to be a rare event going forward since baseline visits will now be allowed remotely, but rarely occurred previously due to prior COVID-19 related delays in Prevention Center scheduling and patient concern about visit timing.

7.5 Duration of Follow-Up

Refer to section 8.0 for the evaluations to be done at baseline, during the 24 week intervention, and at the 24 week time point. After the end-of-study visit, there will be no further study assessments or follow-up. Participants who are randomized to the control arm will be offered the delayed exercise intervention after 24 weeks (which will include a one-on-one session with the exercise physiologist and weekly telephone support), but this intervention is optional, and in addition, there will not be any other assessments or clinic visits.

7.6 Dosing Delays/Dose Modifications

If a participant has a suspected injury as a result of exercise, she will be assessed by a physician. Subsequent exercise will either be held to allow for recovery, or modified, depending on the nature of the injury and physician assessment. If a medical issue develops which is not related to exercise, the exercise prescription will also be modified if needed.

Participants who are receiving maintenance chemotherapy may exercise, but have a few special considerations:

- If a participant develops anemia, she will notify the exercise physiologist and the exercise prescription may be modified. She may need to decrease the intensity or amount of exercise.
- Individuals with a hemoglobin of less than 8 will be instructed to hold exercise until their anemia is improved above this threshold.
- Individuals with neutropenia (low white blood cell count) may have a reduced ability to fight infection and will take precautions (for example, use caution in public exercise facilities, ensure proper cleaning and sterilization of equipment).
- Individuals with a fever (temperature >100.4 degrees Fahrenheit) will avoid exercise until they have not had any further fevers for 24 hours.

- Individuals with low platelet count may have increased risk of bleeding or bruising; they will avoid contact sports or activities with a high risk of falling if platelets are less than 100,000, but may continue other physical activities. They will abstain from exercise if their platelet count is <50,000. Exercise may be resumed when platelets return to above this threshold.

7.7 End of Treatment (EOT) Visit Schedule and Procedures

Subjects who discontinue from the study will not require a clinic visit. They may continue their usual clinical care with their treating physicians. The reason for study discontinuation will be recorded. Participants who desire to stop exercising will be asked whether or not they are willing to complete study assessments. If they are willing, they will complete originally planned study assessments (including clinic visit) at the originally specified time points.

7.8 Emergency Unblinding Procedures

- *Not applicable*

8.0 SUBJECT EVALUATION

8.1 On-Study Clinical Evaluations

Clinical evaluations take place according to the Study Calendar (Appendix C). Baseline assessments will occur prior to randomization, and whenever possible no later than 1 month after informed consent is signed. End-of-study assessments will occur at 24 weeks. The window between this end-of-study visit should be as close to 24 weeks as possible. The study team will make every effort to schedule this visit between 22 weeks and 26 weeks. Baseline and end-of-study visits originally were conducted at the FHCRC Prevention Center. Due to the COVID-19 pandemic and desire to expand clinical trial access to those who are unable or unwilling to travel to Seattle, participants will now be given a choice to have study assessments performed in clinic at the Prevention Center, or near to home/ at home. Participants desiring to avoid clinic visit will have blood collection performed at a local laboratory and continue to collect saliva at home. Collected blood and saliva will be shipped overnight to the FHCRC Prevention Center for specimen processing and storage. Urine collection, vitals, and anthropometrics will be omitted.

Additional assessments (such as surveys or actigraphy) will be performed at intervals throughout the study, but these assessments will be done at home. These assessments will be scheduled according to the Study Calendar, at the specified time point +- 2 weeks, or as close as possible to that time window.

The following tests and procedures are completed, although not all tests may be done at each assessment point; see the detailed study timeline in Appendix C.

- **Anthropometrics and vitals*:*** Blood pressure, resting pulse, weight (in light clothing but without shoes), height (without shoes), waist (smallest diameter) and hip (largest diameter) circumferences. BMI (kg/m^2) will be calculated as weight (kg) divided by height squared (m^2). Participants who opt against a clinic visit will weigh themselves at home and report to us. If available, a recorded height will be abstracted from medical records, and if not available, self-report from the participant will be used. Vitals and anthropometrics will be omitted.
- **Medication Assessment:** Detailed information on use of medications (prescription and non-prescription, including supplements and vitamins) will be collected by a medical assistant at each clinic visit, including drug name, dose, and frequency of use. Participants will be asked to provide a detailed list of their medications to the best of their ability and they will also bring in all of their medications in their original bottles with labels. Study staff will review this information and interview the participant to obtain an accurate, complete medication list. Participants who opt against a clinic visit will be asked to provide a list of prescription and non-prescription medications including drug name, dose, and frequency of use. Study staff can also abstract information based on photographs of medication labels provided by participants and interview as needed. **Daily Physical Activity Log:** Exercise diaries measure daily exercise reliably and have been validated by comparison with physiological measures of compliance such as VO_2 max (79). Intervention arm participants will complete a daily Physical Activity Log at home throughout the study. They will record type of exercise activity, duration, intensity, location (outdoors/indoors), and whether it was performed alone or with others. Participants will complete the Physical Activity Logs either online or on paper; participants completing the Physical Activity Logs on paper will mail them to the study coordinator each week (in stamped addressed envelopes provided by the study).
- **Actigraphy**: Participants will wear a monitor continuously for one week (except during showers/bathing and swimming) at the specified time points. Since self-report may lead to overestimation of exercise adherence, the use of actigraphy to objectively measure exercise intensity and amount adds significant strength to our study (80). Actigraphy will also allow a preliminary evaluation of a dose-response relationship between exercise and our outcomes of interest, and will measure sleeping habits, of interest since sleep disturbances are prevalent in cancer survivors (81). The actigraph will be worn around the waist. Participants will be mailed the actigraph prior to the assessment point, along with instructions, and will mail it back to the study coordinator after the week of use. The actigraph data will be downloaded and the actigraphs will be cleaned using alcohol swabs prior to being mailed back for next use.

Questionnaires *(Appendix D) – all questionnaires will be completed at baseline, 12, and 24 weeks, unless specifically noted. Questionnaires may be completed online through REDCap, or on paper. Paper questionnaires may be mailed with a provided self-addressed stamped envelope or brought to clinic if participant opts for clinic visits.*

- **Demographics, health history, and habits** (Demographics and health history at baseline only): Information will be collected on demographics, medical history, and health habits including medication use, tobacco use, and use of complementary and alternative therapies via a questionnaire.
- **7-day Physical Activity Log:** Participants will complete a seven-day Physical Activity Log (for the preceding 7 days) at baseline (before randomization) and 24-week assessments. Physical Activity Logs of exercise during the seven days preceding the assessment point will be used to determine minutes per week of moderate physical activity.
- Assessment of physical activity prior to ovarian cancer diagnosis (baseline only): Questions 6-8 of Form 34 v2: Personal Habits Questionnaire used by the Women's Health Initiative (https://www.whi.org/researchers/studydoc/_layouts/15/WopiFrame.aspx?sourcedoc=/researchers/studydoc/WHI%20Forms/F034%20v2.pdf&action=default) will be included to assess the participant's estimated level of physical activity in the 2 years prior to their diagnosis of ovarian cancer.
- **Perceived Stress Scale** (82): This instrument uses a Likert-type rating scale to measure the degree to which situations in life are perceived as stressful, specifically unpredictable, uncontrollable, and overloading. The scale has excellent psychometric properties and relates to relevant outcomes in expected ways. Internal consistency is high with Chronbach's alpha's ranging from 0.75 to 0.86.
- **Hospital Anxiety and Depression Scale, anxiety and depression (HADS-A and HADS-D) subscales** (83, 84). This instrument is a well validated and widely used assessment of anxiety and depression. The 14-item scale has two subscales, anxiety and depression, derived from 7 questions each. Participant responses are scored on a scale of 0 to 3 with variable anchors (85). The Internal reliability is high with Chronbach's alpha for the anxiety scale ranging from 0.89-0.93 and 0.86-0.90 for the depression scale (83, 84).
- **The Cancer Worry Scale** is a widely used, four-item scale that assesses the extent to which worry about cancer interferes with daily functioning (86). The items have been adapted to measure worry about cancer recurrence specifically (87). Response options range from 1 ("rarely or not at all") to 4 ("a lot"). The sum of the responses is computed to create a cancer worry score. In a large, community based sample of over 1300 women, the Chronbach's alpha for this scale was 0.73.
- **Health-related Quality of Life:** Health related quality of life will be measured using the RAND 36-Item Short Form Health Survey from the Medical Outcomes Study (88, 89). This survey is a well-validated instrument that assesses eight aspects of health related quality of life and has been used in previous research investigating the effect of exercise on ovarian cancer survivors (90). Specifically, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions are assessed in 36 questions. Participants respond on either a binary yes/no or Likert response scale. Chronbach's alpha is sufficient ranging from 0.78-0.93 for the 8 constructs. Ovarian cancer-specific quality of life will be assessed using the Functional Assessment of Cancer Therapy -Ovarian (FACT-O) (91). The Chronbach's alpha for this scale was 0.92.
- **Fatigue:** will be assessed using the Functional Assessment of Cancer Therapy Fatigue Scale as measures of fatigue have a well-known negative association with quality of life. This scale is a 13-item scale used to assess sleep disturbances and patterns associated with fatigue specifically in cancer patients and survivors (92, 93). Participants respond on a 5-point Likert scale from 0 (not at all) to 5 (very much). It has previously been used to detected significant differences in fatigue among ovarian cancer survivors (94-96). It has acceptable reliability with a Chronbach's alpha of 0.93 and a test-retest correlation of 0.87.
- **Sleep:** The Pittsburgh Sleep Quality Index is a 19-item measure providing a comprehensive picture of sleep quality. Specifically, 7 components representing subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, daytime dysfunction are derived from the scale in addition to an overall global sleep quality score (97, 98). Participant responses range from 0 (no difficulty) to 3 (severe difficulty). Reliability of the scale ranges from 0.77-0.81 and construct validity is sufficiently discriminating (97, 99).
- **Theory of Planned Behavior Constructs:** A 7-item questionnaire developed by Azjen (2006), used to assess the role of TPB in an exercise intervention for ovarian cancer survivors (100), will be used to assess the primary constructs of the Theory of Planned Behavior (101). Each will be measured on a 7-point Likert scale and reflect the intention, attitude, subjective norm, and perceived behavioral control of physical activity. Additionally, underlying beliefs will be assessed with open-ended questions asking about perceived advantages of exercise and barriers to exercise based on Azjen (2006). These assessments will help us understand predictors of adherence to each of the exercise interventions and thus will be used to inform the design of future studies.
- **Food Frequency Questionnaire** (at baseline and 24 weeks only): Persons adopting an exercise program may change their diet, to include increased caloric intake, especially carbohydrates (102, 103). Because dietary changes could be associated with changes in biomarkers, we will obtain accurate baseline and follow-up data on dietary

intake, to document the extent and character of any dietary change. Both intervention and control participants will be carefully counseled that this is not a dietary study, and that they should not significantly change their dietary intake or composition. It will ascertain dietary habits for the preceding month.

Research specific labs

- **Blood specimens**: Blood will be collected for VEGF and IL-6, and will be assayed at the Department of Laboratory Medicine, Children's Hospital Boston, using validated commercial Enzyme Linked Immunosorbent Assays from R&D Systems.(104) We will also collect and store blood for future assays. Participants will be asked to refrain from alcohol, moderate/vigorous exercise (24 hours) or NSAID use (24 hours) prior to a fasting (no food/drink other than water for 12 hours) venous blood collection (up to 50mL), and processed within 1 hour of collection at the FHCRC Specimen Processing lab. Serum and plasma aliquots, buffy coat, packed red blood cells, peripheral blood mononuclear cells, and RNA later collection vials will be stored at -80°C. All specimens will be labeled with the participants' specimen ID number. Participants who opt against a clinic visit will be provided with blood tubes, instructions, and necessary shipping materials to be taken to a local laboratory. They will get their blood drawn at the local laboratory and the local laboratory will process the blood for serum, plasma, and when able, buffy coat per standardized instructions. Other specimens (RNA later, peripheral blood mononuclear cells) will be omitted. Processed specimens will be refrigerated until pick-up and shipped that day (expedited overnight shipping) on ice to the FHCRC Prevention Center for aliquoting and storage by the Prevention Center.
- **Salivary Cortisol:** Participants will collect saliva samples at bedtime for 3 consecutive days at home. They will be asked to refrain from food, drink, caffeine, and exercise for 30 minutes before sample collections, and will be instructed to refrain from brushing or flossing teeth prior to sample collection. They will collect the saliva samples using the "passive drool" method. Sterile cryovials are fitted with a mouthpiece (Saliva Collection Aid) provided in the collection kit (Salimetrics, Carlsbad, CA). Participants are instructed to allow saliva to pool in the mouth. With head tilted forward, participants should drool through the Saliva Collection Aid to collect saliva in the 2 mL cryovial. The procedure is repeated until sufficient sample is collected. They will record the date and time of collection on the vial. Samples will be stored at room temperature by participants, until they can bring samples to the Prevention Center Clinic for their other assessments. At the Prevention Center, they will be placed in the -80°C freezer for long-term storage until assays are ready to be performed. Participants who opt against a clinic visit will be provided with shipping materials, and the samples will be shipped overnight to the Prevention Center and placed in the -80°C freezer for long-term storage until assays are ready to be performed.
- **Urinary norepinephrine**: Participants will collect urine over 24 hours. They will store the urine in provided bottles in their refrigerator (or cooler with ice pack) until they bring the collected urine to the Prevention Center for their clinic visit. At the Prevention Center, the sample volume will be recorded. EDTA (final concentration 1 mM) and sodium metabisulfite (final concentration 4 mM) will be added to the samples in order to prevent catecholamine degredation, and samples will be stored at -80°C. Additional aliquots of untreated urine and urine with boric acid (25ml of urine mixed with 250mg boric acid) will also be stored for possible future assays. 24-hour urine collection may be more valid to assess chronic stress than first-morning void. Participants will receive electronic reminders to collect their urine and saliva samples. Participants who opt against a clinic visit will not perform the 24 hour urine collection due to logistical difficulties associated with shipping urine and processing which is best done immediately rather than delayed.

Assays

- **Duplicate pooled blood, urine, or saliva samples** will be included in each assay batch (~5-10% of samples) for QA and to assess inter- and intra-assay coefficient of variation. Baseline and follow-up samples from each participant will be assayed within each batch (paired), and paired samples will be randomly placed across batches. Laboratory personnel will be blinded with regard to subject and QA sample identity.
- VEGF and IL-6 will be assayed in serum samples at the Clinical and Epidemiologic Research Laboratory, at the Department of Laboratory Medicine, Boston Children's Hospital, Boston, MA, using Enzyme Linked Immunosorbent Assays from R&D Systems (R & D Systems, Minneapolis, MN). We have collaborated with this lab on a variety of studies: in our experience of working with them their assay performance as evaluated by CV and precision in our blind duplicate samples has out-performed other labs that we have worked with in the past, especially in difficult to measure analytes such as cytokines. The lab has extensive experience working with large cohort studies and randomized controlled trials including WHI.
- Cortisol will be assayed from saliva samples at the Salimetrics Lab and Technology Center (Salimetrics, LLC Carlsbad, CA) using the Salimetrics Cortisol ELISA Kit . Salivary cortisol correlates well with serum cortisol levels

(105). Salimetrics specializes in salivary biomarker assays, and in the development of saliva collection protocols and vials. Salimetrics has developed a Cortisol Enzyme Immunoassay Kit, a competitive immunoassay specifically designed and validated for the quantitative measurement of salivary cortisol. An independent research study in 2012 measured cortisol levels in 195 saliva specimens using a reference method (mass spectrometry) compared with the most popular immunoassays. The study reported that the Salimetrics assay was the most accurate and reliable of available commercial assays (106).Norepinephrine will be assayed from urine samples at the Department of Laboratory Medicine, Children's Hospital Boston, using the validated Noradrenaline Research Enzyme Linked Immunosorbent Assays from LDN (Labor Diagnostika Nord GmbH & Co.KG, Germany).

9.0 SUBJECT DISCONTINUATION FROM STUDY

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study intervention.

Cancer recurrence does not mandate study discontinuation. If a subject develops cancer recurrence, they may still continue on the study if they are willing and able. Exercise is safe for individuals with cancer who are undergoing active treatments including chemotherapy. The exercise physiologist may alter their exercise prescription as needed based on the individual's functional ability and medical condition. If a participant desires to discontinue the study, she may discontinue the study at any time. If an individual desires to stop exercising but is willing to complete study assessments, she will complete originally planned study assessments (including clinic visit) at the originally specified time points.

An explanation for discontinuing the study is recorded for each subject discontinuing the study on the appropriate CRF/eCRF. Treatment in this study must be discontinued for any of the following reasons:

- if the PI decides to stop the study;
- at Investigator's discretion;
- at the subject's request;
- Grade 4 or life-threatening toxicity (See Section 11, Adverse Events) attributable to study intervention

Target enrollment is 98 participants, accounting for up to 20% drop-out. Power calculations are based on 78 participants. Additional subjects may be enrolled in the study to replace individuals who have dropped out in order to achieve the goal of 78 participants completing the study.

10.0 ADVERSE EVENTS

10.1 Adverse Event

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Medical conditions present at screening (i.e., before the study treatment is administered) are not adverse events and should not be recorded on adverse event pages of the CRFs. These medical conditions should be adequately documented on the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.

10.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

10.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with a moderate exercise program, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed and reported in preclinical or clinical studies.

10.4 Monitoring and Recording Adverse Events

Participants will be monitored for AEs throughout their study surveillance period (24 weeks from baseline for participants in the intervention arm, 48 weeks from baseline for control participants who opt to complete the delayed intervention). The occurrence of an AE may come to the attention of study personnel during the weekly phone interview by the exercise interventionist, by UW study staff personnel conducting telephone reminders for surveys or biospecimen collection, or by a study participant calling the study team. If an SAE comes to the attention of study personnel, the research team at UW will complete an AE form. All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)

- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study intervention, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

10.5 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

10.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- **Definite**: The event follows a reasonable temporal sequence from exposure to the exercise intervention, has been previously described in association with the intervention, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with discontinuation of the exercise intervention and/or re-appears on re-initiating the exercise intervention..
- **Probable**: The event follows a reasonable temporal sequence from exposure to the exercise intervention and has been previously been described in association with the exercise intervention OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- **Possible**: The event follows a reasonable temporal sequence from exposure to the exercise intervention, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- **Unlikely**: Toxicity is doubtfully related to the exercise intervention. The event may be attributable to other factors su**ch as the subject's clinical state, other therapeutic interventions or concomitant medications.**
- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

10.7 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of first exposure to the exercise intervention. AEs with an onset date prior to the first exposure to the exercise intervention will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

10.8 Adverse Event Reporting Requirements

10.8.1 Reporting to Sponsor

Not applicable

10.8.2 Reporting to IRB

The investigator or designee will report events to the FHCRC IRB in accordance with the policies of the IRB.

10.8.3 Institution-Sponsored IND Reporting Requirements

Not applicable

10.8.4 Study Coordinating Center Requirements

Not applicable

10.8.5 FDA Reporting Requirements

Not applicable

11.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

12.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

All participants' identifying information is kept in restricted access, password-protected files; only authorized persons have access to confidential data. Investigators and lab personnel will not have access to any identifying information. Only study-assigned ID number labels are placed on biospecimen aliquots and all data files with participant information contain only a study-assigned ID number, but no names. No data will be published or released in a way in which individuals could be identified. Any data that is shared with other investigators will be stripped of any identifiers.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

Individuals with stage II-IV ovarian cancer (N=98) who have completed primary treatment within one to six months and are in clinical remission will be randomized to a 24-week home-based exercise program or wait-list control. The exercise prescription will consist of 150 minutes of moderate aerobic exercise (the equivalent of brisk walking or higher intensity) per week, with weekly telephone-based support by an exercise physiologist. The control group will continue their usual activities and will be offered the exercise intervention after 24 weeks. Baseline and 24-week assessments will include validated questionnaires assessing distress and health-related quality of life, serum levels of IL-6 and VEGF, salivary cortisol levels measured at bedtime for three consecutive days, and 24-hour urinary norepinephrine levels. Participants will also complete the questionnaires at 12 weeks to provide additional longitudinal data. Compliance to the intervention will be assessed by daily activity logs, actigraphs, and completion of weekly telephone calls.

13.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

Descriptive statistics will be performed for baseline data, and distributions of outcome measures will be characterized using scatterplots, histograms, and summary statistics (e.g., mean, median, standard deviation, quartiles, range) to identify extreme outliers. Outcome variables will be log-transformed if their distributions are not symmetric. We will also examine if these measurements are balanced between the study intervention groups. The primary assessment of the exercise intervention effects will compare the average change from baseline to 24-week follow-up outcome measures (such as SF-36 physical component score) between the exercise group and the control group. Analyses will be intention-to-treat. The generalized estimating equations (GEE) modification of linear regression will be used in order to model the relationship between the outcome measures and exercise intervention and to account for the correlation within individual data over time. The GEE model will adjust for the measurement time and other potential covariates. Prior to fitting the GEE model, logarithmic transformation will be applied (if appropriate) to the outcome data to achieve approximate normality and variance stabilization. Our statistical inference on each outcome will use the standard large-sample approximation, namely, two-sided Z-test and Z-confidence intervals based on the limiting Gaussian distribution. More specifically, for the primary comparison between exercise group *vs*. control group, let Y_{ij} be the outcome measure (or log-transformed if appropriate) of interest for participant i at time j, where j is 0 for baseline and 1 for 24 week follow-up, X_i be the indicator variable for the intervention status (1=intervention, 0=control) and $\mathbf{Z}_i$ represent a vector of other potential adjusting variables (such as age, BMI). The linear model is as follows:

$E[Y_{ij}] = \alpha_0 + \alpha_1 j + \beta_0 X_i + \beta_1 X_i j + \boldsymbol{\gamma}^T \mathbf{Z}_i$, $Var[Y_{ij}] = \sigma^2$ and $Cov[Y_{ij},Y_{kl}] = \rho$ if i = k and $j \neq l$, and 0 otherwise.

The parameter β_1 is of our main interest and represents the mean difference in the outcome change from baseline to follow-up between participants in the exercise group and participants in the control group, adjusting for covariates **Z** such as age and BMI. We will first assess β_1 without any adjustments for **Z** (unadjusted analysis), and then add **Z** (adjusted analysis). Under the null hypothesis of no difference between intervention and control on the changes in the outcome measure, β_1 is equal to zero. If the exercise intervention indeed results in a greater reduction/increase in the outcome measure of interest in the exercise group compared with the control group, then β_1 is different from zero. Our statistical inference on β_1 will use the standard large-sample approximation, namely, two-sided Z-test and Z-confidence intervals based on the limiting Gaussian distribution.

Our analysis will be based primarily on intention-to-treat principle, but with minor modifications for practical considerations. The principles of ITT analyses are (i) keep participants in the intervention groups to which they were randomized, regardless of the intervention they actually received; (ii) measure outcome data on all participants; and (iii) include all randomized participants in the analysis (107). However, if data of individuals are lost, or are unavailable for other reasons immediately after randomization, then we will not include these individuals in the analysis (modified intention-to-treat). Under the modified intention-to-treat principle, enrolled participants who were later found to be ineligible will not be included in the primary analysis. To take adherence into account, we will also perform per-protocol analysis which includes only individuals who are considered adherent to the intervention assignment. Per-protocol analysis will not be our primary analysis, and we will report in detail the criteria for exclusion of individuals.

If we encounter missing data due to drop out or assay issues, we will apply mixed model regression using the available data in the analysis. In general, our analysis based on available data will be similar to the analysis using the individuals who do not have missing data (complete-case analysis) if the missing data mechanism is completely at random (108). When the

missing data mechanism is at random (MAR), regression imputation and weighted using inverse selection probability are in general the same (109). Hence, under MAR we plan to perform regression imputation or multiple imputation in the analysis. However, missing data may be informative with a nonignorable missing (NIM) mechanism in the sense that the missing data mechanism may be related to the unobserved missing data. When the data may be NIM, we will consider weighted estimation (110), and sensitivity analysis under different assumptions about the missing data. The sensitivity analysis will include, but not restricted to, approaches under the last observation carry forward. We will also apply pattern mixture models for sensitivity analysis to address informative missing data. We will examine the missing data mechanism, and investigate if the regression association among individuals with and without missing data, respectively.

13.3 Sample Size and Power

98 individuals will be randomized. Accounting for up to 20% drop-out, power calculations are based on 78 participants.

Table 1. Minimum detectable absolute difference in mean change from baseline to 24 weeks between two groups (n=39 for Control group and n=39 for Exercise group) for the study endpoints, given an intra-individual correlation (ñ) of 0.5, 0.65 or 0.8, at 80% power, and adjusting for the number of hypotheses tests with 7 primary endpoints (type I error of 0.05/7).

			Minimum detectable absolute difference (% change)		
Endpoint	**Mean**	**SD**	**ñ = 0.5**	**ñ = 0.65**	**ñ = 0.8**
Distress (Perceived Stress Scale)[a]	19.23	6.77	5.41 (28.16%)	4.53 (23.56%)	3.42 (17.81%)
Distress (Hospital Anxiety and Depression Scale-anxiety subscale)[b]	7.4	3.9	3.12 (42.15%)	2.61 (35.27%)	1.97 (26.66%)
Distress (Hospital Anxiety and Depression Scale-depression subscale)[b]	5.8	3.5	2.87 (48.26%)	2.346 (40.4%)	1.77 (30.52%)
Quality of Life (36-item Short Form Survey- Physical Component Score)[c]	45.6	9.2	7.36 (16.14%)	6.16 (13.5%)	4.65 (10.21%)
Il-6 (pg/mL)[d]	2	0.7	0.56 (27.99%)	0.47(23.42%)	0.35 (17.70%)
VEGF (pg/mL)[e]	192	158.2	126.5 (65.88%)	105.8 (55.12%)	80(41.67%)
Salivary cortisol (nmol/L)[d]	4	0.6	0.48 (12.0%)	0.4 (10.04%)	0.3 (7.59%)

Mean and SD obtained from: [a] Perceived Stress Scale score in ovarian cancer survivors at the end of primary chemotherapy (111), [b] Hospital Anxiety and Depression Scale anxiety and depression subscale scores in ovarian cancer survivors towards end of primary chemotherapy (112), [c] 36-item Short Form Survey- Physical Component Score in our randomized controlled trial of exercise in ovarian cancer survivors (17), [d] biomarker levels in ovarian cancer survivors 6 months after primary treatment(113), and [e] VEGF levels in ovarian cancer survivors after completion of primary chemotherapy (114).

13.4 Randomization

After baseline assessments are complete, participants will be randomized with equal probability to the exercise intervention (N=49) or wait-list control (N=49). Randomization will be blocked on stage (stages II-IIIA vs. IIIB-IV) and body mass index (<30 kg/m^2 vs. ≥30 kg/m^2) and will use permuted blocks with random size.

13.5 Additional Efficacy Hypotheses, Outcome Measures, and Statistical Methods

Our exploratory analyses will investigate the effect of the moderate exercise intervention on 24-hour urinary norepinephrine levels. We will use the above GEE model in this investigation to compare the mean changes from baseline to 24-weeks between the exercise intervention and control groups. We will assess the relationships between the change from baseline to 24 weeks in each of the distress or quality of life measures and change from baseline to 24 weeks in each of the biomarkers (IL-6, VEGF, salivary cortisol, urinary norepinephrine) based on the Pearson correlation. Also, we will investigate the association between changes in the outcomes from baseline to 24 weeks (distress, Quality of Life, biomarkers) and exercise adherence among participants in the intervention group. We will provide the mean change in the outcome by category of exercise adherence (≥150 min/week, 120-149 min/week, 90-119 min/week, 60-89 min/week, 30-59 min/week, and <30 min/week).

13.6 Analysis of Covariates

Descriptive statistics will be performed for baseline covariate data, including summary statistics (e.g., mean, median, standard deviation, quartiles, range) to identify extreme outliers. We will examine if covariates are balanced between study groups.

13.7 Exploratory Analysis

In exploratory subgroup analyses, we will apply the GEE models for the primary analysis given above to study the intervention effect on each of the primary outcomes among participants who developed (versus those who did not develop) recurrence over the course of the study. The GEE models will also be applied to additional exploratory subgroup analyses to assess the intervention effects on the primary outcomes by chemotherapy maintenance group (if the sample size is sufficient).

13.8 Ethnic and Gender Distribution Chart

Projected Target Accrual

ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	12	0	12
Not Hispanic or Latino	86	0	86
Ethnic Category Total of All Subjects*	98	0	98
Racial Categories			
American Indian / Alaska Native	2	0	2
Asian	8	0	8
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	4	0	4
White	67	0	67
More Than One Race	4	0	4
Racial Categories: Total of All Subjects*	98	0	98

14.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendix F).

15.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

15.1 Documentation

The documentation of clinical data must be stored by the investigative team according to legal requirements. The PI and study staff has responsibility for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor, the FDA, and/or other applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, site, and Sponsor.

15.2 Access to Source Data

The PI will permit the Sponsor's representatives to monitor the study as frequently as the Sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. The CRF/eCRF and related source documents will be reviewed in detail by the Sponsor's representative at each site visit. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRF/eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with the Sponsor and the Competent Authorities, and IRB/EC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of the FDA or other regulatory agencies.

15.3 Data Collection

Data are collected from medical record review (baseline EMR review CRF), biospecimen analysis (blood, urine, saliva), actigraphy, or patient reported (surveys or physical activity log)

Electronic case report forms must be completed and submitted for each subject enrolled in the study. All data fields in the CRF/eCRF must be completed to avoid queries.

15.4 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval.

15.5 Disclosure of Data/Publication

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by the FDA or other regulatory agencies, the Sponsor or its designee and by the IRB/EC.

15.6 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

15.7 Informed Consent

The PI assumes the responsibility of obtaining written Informed Consent for each subject.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects will receive a comprehensive explanation of the proposed treatment, including the nature

of the therapy, alternative therapies available, any known previously experienced adverse reactions, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Participants will be recruited either in person or via telephone. In-person visits will occur at a regularly scheduled up follow up visit with their provider. For consents on the phone, potential participants will be mailed a recruitment packet consisting of a study introductory letter, 2 copies of the consent, and 2 copies of the HIPAA. A research staff member from the University of Washington will contact the potential participant via telephone to (1) further screen for eligibility and (2) conduct the informed consent process.

For those patients who do not have an appointment within the eligibliity window, study PI or patients' personal oncologist or care team may call the patient to inform them of the study. As a part of routine clinical care, patients would be receiving similar calls if an opportunity for treatment or clinical trial arose. Call would cover basic study information and contact information for more details; detailed questions and any specific eligibility or informed consent conversation would occur with UW research staff.

Study flyers may also be hung in places including UW Medical Center and participating facilities, potentially including on their web site, with contact information in case patients want to self-refer. Flyers may also be hung in ovarian cancer support groups or on their web site, with their permission. Study materials will be posted on UW's website and on social media platforms (e.g., Twitter, Facebook) as well as potentially additional online forums such as cancer survivor groups. The study team will not reach out to individuals on social media; the team will contact groups to ask them to share study information.

Patients may learn of the study through the sources mentioned above and/or from their clinicians, and for patients who self-refer to the study, the following recruitment pathway will apply: Interested patients will self-refer to the study via phone or email, and RCs will obtain their contact information/address in order to mail study information (e.g., flyer) and a medical records release form. Once the signed medical release form is returned to the study team, staff will begin obtaining medical records from relevant facility/facilities. Once medical records are sent to study team, RCs will screen patients' records for eligiblity. Any questions, as with other medical records screening, will be directed to study PI. Patients who pass medical record screening will then be sent the study introductory packet and receive calls to complete phone screening and discuss consent with those interested (the same process as patients referred by clinicians and identified through current screening procedures). Interested patients who become aware of the study through other means (e.g., physicians, social media, or web site) for whom study team does not have EMR access will be contacted by study team to complete an initial phone screening of prioritized eligibility items before medical records are requested, and the above process may differ slightly in order.

All interested patients, regardless of pathway, will have both completed a medical records and telephone screening process before they are consented.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The form is to be signed and dated by the subject and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

Informed Consent may alternatively be documented electronically using the REDCap e-consent module, following all other screening and consent steps described above. Please see attached waivers for documentation of consent and HIPAA per FHCRC IRB's policy.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

15.8 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior Sponsor and IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The PI or designee must promptly notify the IRB/EC of any SAE occurring at the site and of any safety reports (e.g., IND Safety Reports) received from the Sponsor, or its designee.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

15.9 Subject Privacy

The Sponsor and the Investigator affirm and uphold the principle of the subject's right to privacy. The Sponsor, its designates and the Investigator shall comply with applicable national and local privacy laws.

To verify compliance with this protocol, the Sponsor, or its designee, will require that the Investigator permit the Sponsor, or its designee's monitor to review the subject's original medical records. Should access to such medical records require a waiver or authorization separate from the statement of Informed Consent, the Investigator will obtain such permission in writing from the subject before the subject is entered into the study.

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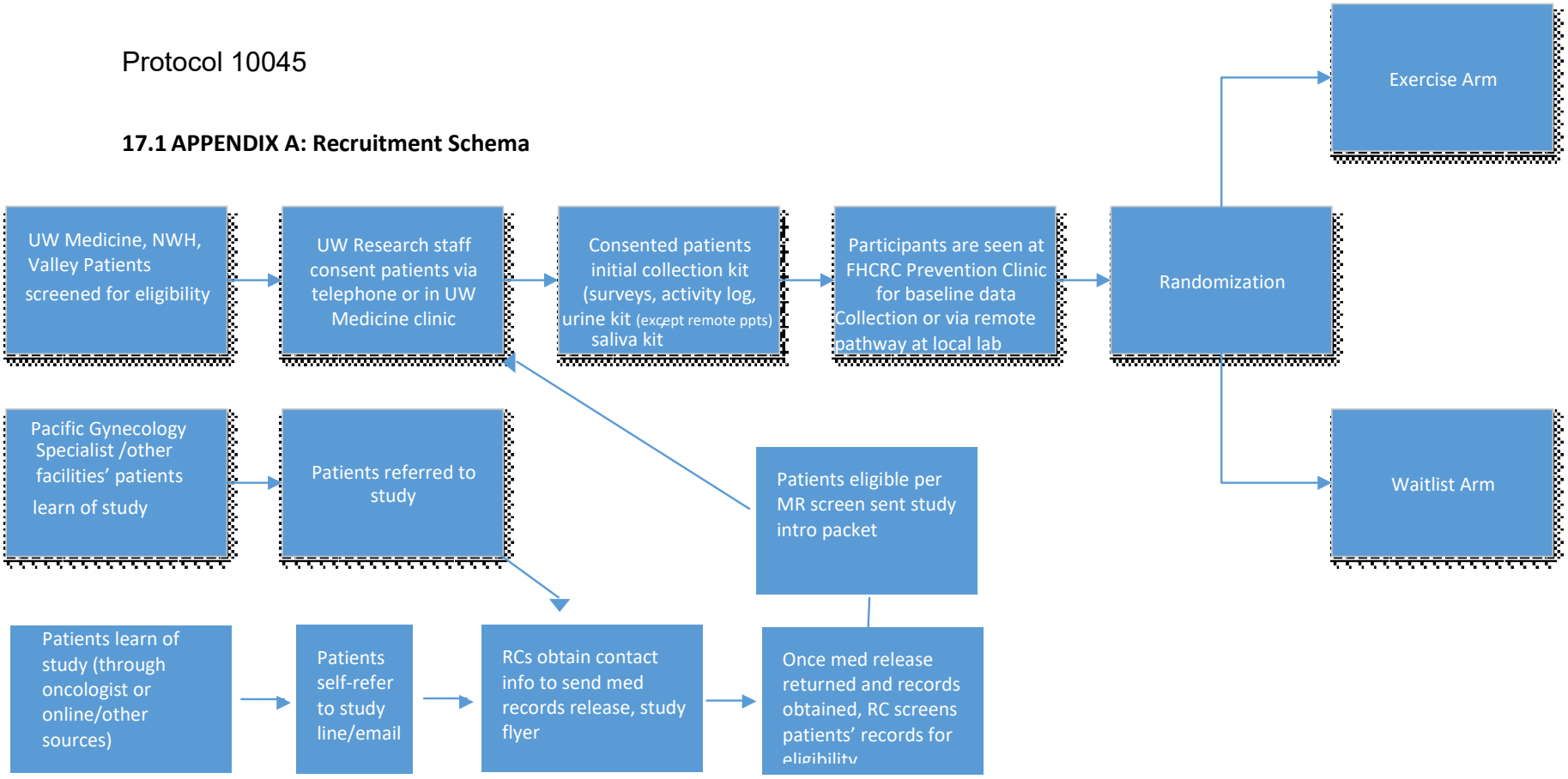
17.0 APPENDICES

Appendix A: Recruitment Schema
Appendix B: ECOG Performance Status Scale
Appendix C: Study Calendar
Appendix D: Questionnaire
Appendix E: Physical Activity Log
Appendix F: Informed Consent Form

17.1 APPENDIX A: Recruitment Schema



17.2 APPENDIX B: ECOG Performance Status Scale

ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

17.3 APPENDIX C: Study Calendar

Study Calendar

		Week 0 (study start)	Week 8	Week 12	Week 16	Week 24
Clinic Visit (with vitals and anthropometrics, medication assessment, saliva and urine, and blood collection)*	Exercise Group	✓				✓
	Waitlist Group	✓				✓
Questionnaires	Exercise Group	✓		✓		✓
	Waitlist Group	✓		✓		✓
Exercise Training followed by weekly calls	Exercise Group	✓				
	Waitlist Group					✓
Daily Physical Activity Log	Exercise Group	✓	✓	✓	✓	✓
	Waitlist Group					✓
Physical Activity Monitor	Exercise Group	✓	✓	✓	✓	✓
	Waitlist Group	✓				✓

*Due to COVID-19 pandemic and desire to expand access to those who are unable to travel to Seattle, participants will be given a choice to have study assessments performed in clinic at the Prevention Center (if they are willing and able to travel to clinic), or near to home. Participants desiring to avoid clinic visit will have blood collection at a local laboratory and continue to collect saliva at home. Collected blood and saliva will be shipped overnight to the FHCRC Prevention Center. Urine collection, vitals, and anthropometrics will be omitted.

Appendix D: Baseline Questionnaire

Exercise Study for Ovarian Cancer Survivors
Baseline Questionnaire

PARTICIPANT ID: _____ DATE COMPLETED: _____/_____/_____

Please complete this questionnaire to the best of your ability. You may skip any questions that you do not feel comfortable answering. This assessment is for research purposes only and the information provided will not be shared with your healthcare providers.

Please note that confidentiality by email cannot be guaranteed and standard text-messaging rates apply

Name:

_____

First Name *(Preferred Name)* *Last Name*

Mailing Address:

_____

City *State*

ZIP code

Email addresses: _____ _____

Personal email *Work email*

Phone Contact: _____ _____ _____

Home Phone *Cell Phone* *Work Phone*

Do we have permission to text you at your cellphone number?

☐ Yes ☐ No

What is the best number to reach you?

☐ Home ☐ Cell ☐ Work

What is the best time to reach you by phone?

Morning (____:____ AM) Afternoon (____:____ PM) Evening (____:____ PM)

What is the earliest and latest we could call you?

(____:____ AM) (____:____ PM)

Alternate Contact:

First and Last Name: _____

Phone Number: _____

Relationship: _____

<u>Demographics and health</u>

1. **Are you of Hispanic, Latino, or Spanish origin?** *For example: Mexican, Mexican American, Puerto Rican, Cuban, Argentinean, Colombian, Dominican, Nicaraguan, Salvadoran, Spaniard, and so on.*
   - ☐ Yes
   - ☐ No

2. **What is your race?***:*
   - ☐ White
   - ☐ Black or African American
   - ☐ American Indian or Alaska Native
   - ☐ Asian
   - ☐ Native Hawaiian or other Pacific Islander
   - ☐ Other, please specify:_____

3. **Is English the primary language spoken in your household?**
   - ☐ Yes
   - ☐ No, the primary language is Spanish
   - ☐ No, the primary language is:

     _____

4. **What is your current marital status?**
   - ☐ Married
   - ☐ Divorced
   - ☐ Widowed
   - ☐ Separated
   - ☐ Single, never married
   - ☐ Unmarried, living with partner

5. **What is the <u>highest</u> education level that you have attained?**
   - ☐ Less than high school
   - ☐ High school graduate or GED
   - ☐ Some college, no degree
   - ☐ Occupational/technical/vocational program
   - ☐ Associate degree: academic program
   - ☐ Bachelor's degree
   - ☐ Master's degree (e. g. MA, MS, MEng, MBA)
   - ☐ Professional school degree (e. g. MD, DDS, DVM, JD)
   - ☐ Doctoral degree (e. g. PhD)

6. **What is your current employment status?** (*check one)*
   - ☐ Employed, full-time
   - ☐ Employed, part-time
   - ☐ Employed, but on sick leave
   - ☐ Unemployed, looking for work
   - ☐ Unemployed, NOT looking for work
   - ☐ Disabled
   - ☐ Student
   - ¨ Retired
   - ☐ Other, *specify:*

     _____

7. **If employed, do you work outside of the home?**
   - ☐ Yes
   - ☐ No
   - ☐ Not employed

8. **If employed, how often does your job require a lot of physical activity during your work shift?** *(check one)*
   - ☐ All of the time
   - ☐ Most of the time
   - ☐ Some of the time
   - ☐ A little of the time

☐ Never
☐ Not employed

9. **Have you ever smoked?** ☐ Yes ☐ No

If yes:

a. Have you smoked a total of 100 or more cigarettes in your lifetime? ☐ Yes ☐ No

b. Do you currently smoke cigarettes regularly?

☐ No
☐ Yes, how many cigarettes per day:
☐ < 5 cigarettes per day
☐ 5-9 cigarettes per day
☐ 10-20 cigarettes per day
☐ >20 cigarettes per day

10. Do you currently vape or use e-cigarettes?

☐ Yes, how many e-cigarettes or how much e-liquid per day? _____
☐ No

11. Have you ever been told by a physician that you have any of the following conditions? *Please check all that apply:*

☐ Depression, *if yes, please check all that apply:*
☐ Current
☐ Past
☐ Anxiety, *if yes, please check all that apply:*
☐ Current
☐ Past
☐ Diabetes, *if yes, controlled with*:
☐ Diet
☐ Insulin
☐ Non-insulin medications
☐ High blood pressure
☐ High cholesterol
☐ Thyroid disease, *if yes:*
☐ Overactive
¨ Underactive
☐ Osteoporosis or osteopenia (thin bones)
☐ Stroke or transient ischemic attack (TIA), *if yes, at what age?* _____
☐ Peripheral vascular disease
☐ Cancer (besides ovarian, fallopian tube, peritoneal), *if yes, what kind and when?*_____
☐ COPD or emphysema
☐ Asthma
☐ Other lung disease, *if yes, what kind?* _____
☐ Sleep apnea (OSA)
☐ Abnormal kidney function
☐ Other kidney disease, *if yes, what kind?* _____
☐ Cirrhosis of the liver
☐ Autoimmune disorder, *if yes, what kind?* _____
☐ Prior organ transplant, *if yes, what kind?* _____
☐ Immunosuppression, *if yes, please check all that apply:*
☐ HIV/AIDS

☐Chronic steroid use
☐ Other(*please list):* _____

☐ Crohn's disease or ulcerative colitis
☐ Irritable bowel syndrome
☐ Seizures
☐ Deep venous thrombosis (DVT) or pulmonary embolism (PE) (blood clot in leg or lungs)
☐ Implantable device, *if yes, what kind?* _____
☐ Chronic pain
☐ Fibromyalgia
☐ Arthritis, if yes, where? _____
Severity: ☐ mild
☐ moderate
☐ severe
☐ Other major medical problems besides heart problems (which we already asked you about), *please list*:_____

12. Do you currently regularly experience any of the following? Check all that apply:

☐ Lymphedema
Severity: ☐ mild
☐ moderate
☐ severe
☐ Peripheral neuropathy
Severity: ☐ mild
☐ moderate
☐ severe

13. Thinking about your day to day life, do you walk:

☐ Independently
☐ With assistive device (cane/walker)

14. Are you currently regularly taking any of the following pain medications (*check all that apply*):

☐ Aspirin or drugs that contain aspirin
☐ Acetaminopen (tylenol)
☐ Pain relievers or anti-inflammation drugs, such as Ibuprofen (Advil, motrin, Nuprin), Naproxen (Naprosyn, Aleve, Anaprox)
☐ COX-2 inhibitors such as celecoxib (Celebrex) or Rofecoxib (Vioxx), other?
¨ Pain relievers that contain narcotics, such as oxycodone, hydrocodone, hydromorphone (Dilaudid), morphine, fentanyl, other?

15. Do you currently regularly engage in any of the following therapies (*check all that apply*):

☐ Acupuncture
☐ Chiropractic therapy
☐ Massage therapy
☐ Yoga, Tai Chi, or Qi Gong
☐ Meditation or deep breathing
☐ Energy therapy, such as Reiki or Healing Touch
☐ Naturopathy and/or herbal medicine
☐ Aromatherapy
☐ Reflexology
☐ Homeopathy
☐ Other complementary or alternative therapies, *please list:* _____

Short Form – 36

16. In general, would you say your health is:

☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor

17. Compared to one year ago, how would you rate your health in general now?

☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
18. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
19. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
20. Lifting or carrying groceries	☐	☐	☐
21. Climbing several flights of stairs	☐	☐	☐
22. Climbing one flight of stairs	☐	☐	☐
23. Bending, kneeling, or stooping	☐	☐	☐
24. Walking more than a mile	☐	☐	☐
25. Walking several blocks	☐	☐	☐
26. Walking one block	☐	☐	☐
27. Bathing or dressing yourself	☐	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

	Yes	No
28. Cut down the amount of time you spent on work or other activities	☐	☐
29. Accomplished less than you would like	☐	☐
30. Were limited in the kind of work or other activities	☐	☐
31. Had difficulty performing the work or other activities (e. g. it took extra effort)	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
32. Cut down the amount of time you spent on work or other activities	☐	☐
33. Accomplished less than you would like	☐	☐
34. Didn't do work or other activities as carefully as usual	☐	☐

35. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

36. How much bodily pain have you had during the past 4 weeks?

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

37. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closes to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
38. Did you feel full of pep?	☐	☐	☐	☐	☐	☐
39. Have you been a nervous person?	☐	☐	☐	☐	☐	☐
40. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
41. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
42. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
43. Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
44. Did you feel worn out?	☐	☐	☐	☐	☐	☐
45. Have you been a happy person?	☐	☐	☐	☐	☐	☐
46. Did you feel tired?	☐	☐	☐	☐	☐	☐

47. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

How TRUE or FALSE is each of the following statements for you.

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
48. I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
49. I am as healthy as anybody I know	☐	☐	☐	☐	☐
50. I expect my health to get worse	☐	☐	☐	☐	☐
51. My health is excellent	☐	☐	☐	☐	☐

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate how often you felt or thought a certain way.

	Never	Almost Never	Sometimes	Fairly Often	Very Often

52.	In the last month, how often have you been upset because of something that happened unexpectedly?	☐	☐	☐	☐	☐
53.	In the last month, how often have you felt that you were unable to control the important things in your life?	☐	☐	☐	☐	☐
54.	In the last month, how often have you felt nervous and “stressed”?	☐	☐	☐	☐	☐
55.	In the last month, how often have you dealt successfully with irritating life hassles?	☐	☐	☐	☐	☐
56.	In the last month, how often have you felt you were effectively coping with important changes that were occurring in your life?	☐	☐	☐	☐	☐
57.	In the last month, how often have you felt confident about your ability to handle your personal problems?	☐	☐	☐	☐	☐
58.	In the last month, how often have you felt that things were going your way?	☐	☐	☐	☐	☐
59.	In the last month, how often have you found that you could not cope with all the things that you had to do?	☐	☐	☐	☐	☐
60.	In the last month, how often have you been able to control irritations in your life?	☐	☐	☐	☐	☐
61.	In the last month, how often have you felt that you were on top of things?	☐	☐	☐	☐	☐
62.	In the last month, how often have you been angered because of things that were outside of your control?	☐	☐	☐	☐	☐
63.	In the last month, how often have you found yourself thinking about things that you have to accomplish?	☐	☐	☐	☐	☐
64.	In the last month, how often have you been able to control the way you spend your time?	☐	☐	☐	☐	☐
65.	In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	☐	☐	☐	☐	☐

Hospital Anxiety and Depression Scale

Check the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate is best.

		Most of the time	A lot of the time	From time to time, occasionally	Not at all
66.	I feel tense or 'wound up'	☐	☐	☐	☐
67.	I feel as if I am slowed down	☐	☐	☐	☐
68.	I still enjoy the things I used to enjoy	☐	☐	☐	☐
69.	I get a sort of frightened feeling like 'butterflies' in the stomach	☐	☐	☐	☐
70.	I get a sort of frightened feeling as if something awful is about to happen:	☐	☐	☐	☐
71.	I have lost interest in my appearance	☐	☐	☐	☐
72.	I can laugh and see the funny side of things	☐	☐	☐	☐
73.	I feel restless as I have to be on the move	☐	☐	☐	☐
74.	Worrying thoughts go through my mind:	☐	☐	☐	☐
75.	I look forward with enjoyment to things	☐	☐	☐	☐
76.	I feel cheerful	☐	☐	☐	☐
77.	I get sudden feelings of panic	☐	☐	☐	☐
78.	I can site at ease and feel relaxed	☐	☐	☐	☐
79.	I can enjoy a good book or radio or TV program	☐	☐	☐	☐

Physical Activity Log (over the last week)

During the last 7 days, please list any moderate-intensity exercise you have done (such as jogging, aerobics, **fast** walking, cycling) **that increase your heart rate and cause you to sweat.** For each day, please list the activities performed and total duration (in minutes) of the physical activity.

Monday	Total Minutes: _____ Type of Exercise(s): _____
Tuesday	Total Minutes: _____ Type of Exercise(s): _____
Wednesday	Total Minutes: _____ Type of Exercise(s): _____
Thursday	Total Minutes: _____ Type of Exercise(s): _____
Friday	Total Minutes: _____ Type of Exercise(s): _____
Saturday	Total Minutes: _____ Type of Exercise(s): _____
Sunday	Total Minutes: _____ Type of Exercise(s): _____

Physical Activity Level Prior to Diagnosis of Ovarian Cancer

The following questions are about your usual physical activity and exercise (this includes walking and sports) **BEFORE you were diagnosed with ovarian cancer**.

For the following questions, please answer according to your typical physical activity that you did approximately **TWO YEARS BEFORE YOUR DIAGNOSIS OF OVARIAN CANCER.**

80) Think about the walking you did outside the home. How often did you walk outside the home for more than 10 minutes without stopping? (Mark only one)

☐ Rarely or never
☐ 1-3 times each month
☐ 1 time each week
☐ 2-3 times each week
☐ 4-6times each week
☐ 7 or more times each week

80.1) When you walked outside the home for more than 10 minutes without stopping, for how many minutes did you usually walk?

☐ Less than 20 minutes
☐ 20-39 minutes
☐ 40-59 minutes
☐ 1 hour or more

80.2) What was your usual speed?

☐ Casual strolling or walking (less than 2 miles an hour)
☐ Average or normal (2-3 miles an hour)
☐ Fairly fast (3-4 miles an hour)
☐ Very fast (More than 4 miles an hour)
☐ Don't know

81) Not including walking outside the home, how often each week (7 days) did you usually do the exercises below?

81.1) STRENUOUS OR VERY HARD EXERCISE (You work up a sweat and your heart beats fast.) For example, aerobics, aerobic dancing, jogging, tennis, swimming laps.
☐ None
☐ 1 day per week
☐ 2 days per week
☐ 3 days per week
☐ 4 days per week
☐ 5 or more days per week

81.2) How long did you usually do exercise like this at one time?
☐ Less than 20 minutes
☐ 20-39 minutes
☐ 40-59 minutes
☐ 1 hour or more

81.3) MODERATE EXERCISE (Not exhausting). For example, biking outdoors, using an exercise machine (like a stationary bike or treadmill), calisthenics, easy swimming, popular or folk dancing.
☐ None

☐ 1 day per week
☐ 2 days per week
☐ 3 days per week
☐ 4 days per week
☐ 5 or more days per week

81.4) How long did you usually do exercise like this at one time?
☐ Less than 20 minutes
☐ 20-39 minutes
☐ 40-59 minutes
☐ 1 hour or more

81.5) MILD EXERCISE For example, slow dancing, bowling, golf.
☐ None
☐ 1 day per week
☐ 2 days per week
☐ 3 days per week
☐ 4 days per week
☐ 5 or more days per week

81.6) How long did you usually do exercise like this at one time?
☐ Less than 20 minutes
☐ 20-39 minutes
☐ 40-59 minutes
☐ 1 hour or more

82) Approximately TWO YEARS BEFORE YOUR DIAGNOSIS OF OVARIAN CANCER, did you usually do strenuous or very hard exercises at least 3 times a week? This would include exercise that was long enough to work up a sweat and make your heart beat fast.
☐ No
☐ Yes

FACT-O
English (Universal) 16 November 2007

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days.</u>**

			Not at all	A little bit	Some-what	Quite a bit	Very much
		<u>PHYSICAL WELL-BEING</u>					
GP1	**83)**	I have a lack of energy	0	1	2	3	4
GP2	**84)**	I have nausea	0	1	2	3	4
GP3	**85)**	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	**86)**	I have pain	0	1	2	3	4
GP5	**87)**	I am bothered by side effects of treatment	0	1	2	3	4
GP6	**88)**	I feel ill	0	1	2	3	4
GP7	**89)**	I am forced to spend time in bed	0	1	2	3	4

			Not at all	A little bit	Some-what	Quite a bit	Very much
		<u>SOCIAL/FAMILY WELL-BEING</u>					
GS1	**90)**	I feel close to my friends.....	0	1	2	3	4
GS2	**91)**	I get emotional support from my family	0	1	2	3	4
GS3	**92)**	I get support from my friends.....	0	1	2	3	4
GS4	**93)**	My family has accepted my illness	0	1	2	3	4
GS5	**94)**	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	**95)**	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1		*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	**96)**	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days.</u>

EMOTIONAL WELL-BEING

			Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	**97)**	I feel sad	0	1	2	3	4
GE2	**98)**	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	**99)**	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	**100)**	I feel nervous.....	0	1	2	3	4
GE5	**101)**	I worry about dying	0	1	2	3	4
GE6	**102)**	I worry that my condition will get worse	0	1	2	3	4

FUNCTIONAL WELL-BEING

			Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	**103)**	I am able to work (include work at home)	0	1	2	3	4
GF2	**104)**	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	**105)**	I am able to enjoy life.....	0	1	2	3	4
GF4	**106)**	I have accepted my illness.....	0	1	2	3	4
GF5	**107)**	I am sleeping well	0	1	2	3	4
GF6	**108)**	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	**109)**	I am content with the quality of my life right now.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days.</u>

			Not at all	A little bit	Some-what	Quite a bit	Very much
		ADDITIONAL CONCERNS					
O1	**110)**	I have swelling in my stomach area	0	1	2	3	4
C2	**111)**	I am losing weight.....	0	1	2	3	4
C3	**112)**	I have control of my bowels.....	0	1	2	3	4
O2	**113)**	I have been vomiting.....	0	1	2	3	4
B5	**114)**	I am bothered by hair loss	0	1	2	3	4
C6	**115)**	I have a good appetite	0	1	2	3	4
C7	**116)**	I like the appearance of my body	0	1	2	3	4
BMT5	**117)**	I am able to get around by myself.....	0	1	2	3	4
B9	**118)**	I am able to feel like a woman	0	1	2	3	4
O3	**119)**	I have cramps in my stomach area	0	1	2	3	4
BL4	**120)**	I am interested in sex.....	0	1	2	3	4
BMT7	**121)**	I have concerns about my ability to have children.....	0	1	2	3	4

Cancer Worry Scale

During the past 6 months:

122) How often have you thought about your chances of getting cancer again?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

123) Have these thoughts affected your mood?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

124) Have these thoughts interfered with your ability to do daily activities?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

125) How concerned are you about the possibility of getting cancer one day?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

126) How often do you worry about developing cancer?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

127) How much of a problem is this worry?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

128) How often do you worry about the chance of family members developing cancer?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

129) How concerned are you about the possibility that you will ever need surgery again?

☐[1] Not at all/Rarely ☐[2] Sometimes ☐[3] Often ☐[4] Almost all of the time

Functional Assessment of Chronic Illness Therapy-Fatigue

Below is a list of statements that other people with your illness have said are important. Please mark one number per line to indicate your response as it applies to the past **7 days**.

	Not at all	A little bit	Somewhat	Quite a bit	Very much
130) I feel fatigued	☐	☐	☐	☐	☐
131) I feel weak all over	☐	☐	☐	☐	☐
132) I feel listless ("washed out")	☐	☐	☐	☐	☐
133) I feel tired	☐	☐	☐	☐	☐
134) I have trouble starting things because I am tired	☐	☐	☐	☐	☐
135) I have trouble finishing things because I am tired	☐	☐	☐	☐	☐
136) I have energy	☐	☐	☐	☐	☐
137) I am able to do my usual activities	☐	☐	☐	☐	☐
138) I need to sleep during the day	☐	☐	☐	☐	☐
139) I am too tired to eat	☐	☐	☐	☐	☐
140) I need help doing my usual activities	☐	☐	☐	☐	☐
141) I am frustrated by being too tired to do the things I want to do	☐	☐	☐	☐	☐
142) I have to limit my social activity because I am tired	☐	☐	☐	☐	☐

Pittsburgh Sleep Quality Index

During the past month:

143) When have you usually gone to bed? _____

144) How long (in minutes) has it taken you to fall asleep each night? _____

145) What time have you usually gotten up in the morning? _____

146) How many hours of actual sleep did you get at night? _____

147) How many hours were you in bed? _____

	Not during the past month	**Less than once a week**	**Once or twice a week**	**Three or more times a week**
During the past month, how often have you had trouble sleeping because you:				
148) Cannot get to sleep within 30 minutes	☐	☐	☐	☐
149) Wake up in the middle of the night or early morning	☐	☐	☐	☐
150) Have to get up to use the bathroom	☐	☐	☐	☐
151) Cannot breathe comfortably	☐	☐	☐	☐
152) Cough or snore loudly	☐	☐	☐	☐
153) Feel too cold	☐	☐	☐	☐
154) Feel too hot	☐	☐	☐	☐
155) Have bad dreams	☐	☐	☐	☐
156) Have pain	☐	☐	☐	☐
157) Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s): _____	☐	☐	☐	☐
158) During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
159) During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐
160) During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?	☐	☐	☐	☐
	Very good	**Fairly good**	**Fairly bad**	**Very bad**
161) During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

Theory of Planned Behavior Constructs

The following questions ask you about your past exercise habits and your beliefs, attitudes, and goals for exercise training over the next 6 months. Please answer the questions as though you were assigned to the exercise training group (even though you do not know yet). That is, answer the questions as though you were about to start your 6 month exercise training program. Please also remember that the exercise training program we will ask you to follow consists of 150 minutes per week of moderate intensity aerobic activity, such as brisk walking. *With moderate intensity aerobic exercise, your heart rate should increase slightly, and you can talk but cannot sing. Examples include walking briskly but not jogging, biking less than 10 mph, water aerobics, and ballroom dancing.*

	Extremely Unlikely	**Quite Unlikely**	**Slightly Unlikely**	**Neutral**	**Slightly Likely**	**Quite Likely**	**Extremely Likely**
If I were to complete 6 months of exercise, I would likely…							
162) Improve my energy level	☐	☐	☐	☐	☐	☐	☐
163) Relieve my stress	☐	☐	☐	☐	☐	☐	☐
164) Improve my treatment side effects	☐	☐	☐	☐	☐	☐	☐
165) Reduce my risk of cancer recurrence	☐	☐	☐	☐	☐	☐	☐
166) Lose weight	☐	☐	☐	☐	☐	☐	☐

167) I think that participating in this 6 month exercise program would be. . . .

extremely useless (1)	quite useless (2)	slightly useless (3)	Neutral (4)	slightly useful (5)	quite useful (6)	extremely useful (7)
☐	☐	☐	☐	☐	☐	☐

168)

extremely unenjoyable (1)	quite unenjoyable (2)	slightly unenjoyable (3)	neutral (4)	slightly enjoyable (5)	quite enjoyable (6)	extremely enjoyable (7)
☐	☐	☐	☐	☐	☐	☐

169)

extremely boring (1)	quite boring (2)	slightly boring (3)	Neutral (4)	slightly interesting (5)	quite interesting (6)	extremely interesting (7)
☐	☐	☐	☐	☐	☐	☐

170) For me to complete this 6 month exercise program would be. . . .

extremely easy (1)	quite easy (2)	slightly easy (3)	Moderately easy/difficult (4)	slightly difficult (5)	quite difficult (6)	extremely difficult (7)
☐	☐	☐	☐	☐	☐	☐

171) If I wanted to, I could easily complete this 6 month exercise program.

strongly disagree (1)	moderately disagree (2)	slightly disagree (3)	Neutral (4)	slightly agree (5)	moderately agree (6)	strongly agree (7)
☐	☐	☐	☐	☐	☐	☐

172) How much control do you feel you would have over completing this 6 month exercise program?

Very little control (1)	(2)	(3)	Moderate control (4)	(5)	(6)	Complete control (7)
☐	☐	☐	☐	☐	☐	☐

173) Most people who are important to me <u>think I should</u> do this 6 month exercise program.

strongly disagree (1)	moderately disagree (2)	slightly disagree (3)	Neutral (4)	slightly agree (5)	moderately agree (6)	strongly agree (7)
☐	☐	☐	☐	☐	☐	☐

174) Most people who are important to me <u>approve</u> of me doing this 6 month exercise program.

strongly disagree (1)	moderately disagree (2)	slightly disagree (3)	Neutral (4)	slightly agree (5)	moderately agree (6)	strongly agree (7)
☐	☐	☐	☐	☐	☐	☐

175) My goal would be to complete _____ minutes per week of the 150 minutes per week of moderate intensity aerobic activity, such as brisk walking *(insert a number between 0 and 150)***.**

176) How motivated are you to achieve the above goal?

slightly motivated (1)	(2)	(3)	moderately motivated (4)	(5)	(6)	extremely motivated (7)
☐	☐	☐	☐	☐	☐	☐

177) Most people like me exercised for <u>150 minutes per week</u> in the 1-6 months after surgery and/or chemotherapy for ovarian cancer.

strongly disagree (1)	moderately disagree (2)	slightly disagree (3)	Neutral (4)	slightly agree (5)	moderately agree (6)	strongly agree (7)
☐	☐	☐	☐	☐	☐	☐

178) List the main advantages of exercising at least 150 minutes per week for 6 months at moderate intensity.

179) List what would make it difficult for you to exercise <u>at least 150 minutes per week for 6 months</u> at moderate intensity.

17.4 Food Frequency Questionnaire **[see PDF, included]**

17.5 APPENDIX E: Physical Activity Log

Daily Physical Activity Log Instructions

Use and Importance of the Daily Activity Logs

- The daily physical activity log is a very important component of the exercise program since it is a record of what you are doing.
- Please fill out the physical activity log after each bout of exercise. Each time you fill out the log:

1. Please *write in pen and as neatly as possible* (if you are not filling out the exercise log online).
2. Record your exercise immediately after each session. If you wait to record your exercise until later in the day or the next day, you may forget what the duration or exercise intensity rating was.
3. Please only record the sports/physical activities you participated in (*e.g.,* brisk walking) for at least 10 minutes duration.
4. For each day, please record the following:
    - Total duration of exercise (in minutes).
    - Type of exercise (e.g., brisk walking, cycling, etc.) – if you did multiple types, list each type.
    - Your perceived exercise intensity (record this even if you were also wearing a heart rate monitor).

If you do not remember the Borg Rating of Perceived Exertion scale, it is printed on the back of the exercise log so that you can refer to it as needed.

- If you wore a heart monitor, record your average heart rate (the heart rate that was maintained throughout the majority of exercise) and your maximum heart rate.
- Record whether you exercised indoors or outside.
- Record whether you exercised alone, or if you exercised with a support person (friend, family, other people you like to exercise with).

5. Record any comments, questions, or concerns that you have that you would like to discuss with the exercise physiologist during your weekly telephone call.

6. After you have completed the Physical Activity Log for the whole week, keep it with you so that you can refer to it during your weekly phone call with the exercise trainer. **After your phone call, please place the completed week's exercise log in**

a self-addressed, stamped envelope (which we have provided), and mail it back to us or complete it online.

- During our weekly phone calls, we will ask you about your exercise sessions. **It is very important that the information you provide about your exercise be as accurate as possible.**
- If you found it difficult to exercise, please provide comments as to possible reasons.
- Our goal is simply to encourage daily exercise and identify what some barriers are to being able to exercise.

Borg Rating of Perceived Exertion	Description
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard (heavy)
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Borg RPE Scale -- © Gunnar Borg, 1998, *Borg's Perceived Exertion and Pain Scales, Human Kinetics, Champaign, IL.*

Participant ID: ___ ___ ___ **Week: ___ ___**

Target Minutes: _____ **Date: ___ ___ / ___ ___ / ___ ___ ___ ___**

Target RPE: _____ (MM / DD / YYYY)

Day 1	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg:_____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 2	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg:_____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 3	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**:Avg: _____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 4	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg: _____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 5	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg: _____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 6	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg: _____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)
Day 7	Minutes:_____ Type of Exercise(s): _____ RPE* (6-20):_____ Heart Rate**: Avg: _____Max:_____	Location: ☐ Indoors ☐ Outdoors	Exercised with: ☐ Self only ☐ With other(s)

Rate of Perceived Exertion (RPE) – 6 to 20, with 6 being "resting" and 20 being "very, very strong." See the back of this page for the full RPE scale. ** Record heart rate if wearing a heart monitor

Comments or concerns:

17.6 APPENDIX F: Informed Consent

UNIVERSITY OF WASHINGTON
CONSENT FORM
Ovarian Cancer Exercise Study

Principal Investigator:
Kathryn Pennington, MD, Assistant Professor, UW Gynecologic Oncology 206-543-3669

General Study Contact
Kelsey Pullar, MPH, Senior Project Manager, UW Surgery 206-221-8247

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

You are being asked to take part in this study because you have completed treatment for ovarian cancer. While patients often achieve a remission after initial treatment, the cancer may come back. Individuals with ovarian cancer often experience high levels of distress and multiple side effects such as fatigue, weakness, anxiety, and other symptoms that decrease their quality of life. These symptoms often persist even after treatment is finished. Studies have shown that distress and chronic stress can make cancers grow and spread. We need to develop and study interventions that can both improve quality of life in ovarian cancer survivors and lengthen survival time.

Studies have proven that exercising after completing treatment for other types of cancer can improve quality of life. However, there have been very few studies on the effects of exercise on quality of life or experiences of distress specifically for individuals with ovarian cancer. In addition, we do not know whether physical activity can improve the likelihood of ovarian cancer patients living longer. While studies examining how exercise might affect cancer survival would need to enroll many patients, we can examine the effects of exercise on levels of specific proteins in the blood (biomarkers) in smaller studies. We know that levels of these biomarkers are higher in patients who have poor cancer survival. If we can demonstrate that exercise can lower these biomarkers, it might indicate that exercise can improve survival. Studying how exercise changes these biomarkers can also help us to understand the biological effects of exercise and the specific ways that exercise can improve survival.

We will enroll into our study 98 individuals with ovarian cancer who have undergone surgery and completed chemotherapy within six months, and who are in clinical remission. We will compare the effects of moderate aerobic ("cardio") exercise versus controls (no exercise program) on distress, quality of life, cortisol and norepinephrine (hormones that can be elevated when people feel "stressed"), and biomarkers associated with decreased survival including VEGF and IL-6 (proteins responsible for making tumors more likely to spread and grow). Of enrolled participants, 49 will be randomly assigned to a 6-month home-based, moderate intensity aerobic exercise program and 49 will be randomly assigned into a waitlisted control group.

STUDY PROCEDURES

If you decide to volunteer for the study, you will receive a 6-month home-based exercise program shortly after joining the study or be waitlisted for the exercise program and receive it after the 6-month time point. Participants in the home-based exercise arm will meet in-person or virtually with an exercise trainer to learn how to exercise safely and how to gradually increase their activity level each week to reach the goal of moderate intensity exercise for 150 minutes per week. They will receive weekly telephone calls to help with motivation and to help address any barriers or challenges they are experiencing with exercise. Participants in the waitlist control will be offered the exercise program and support calls after 6 months.

A computer will randomly assign you to either receive the exercise program now or be waitlisted for a future time. You have an equal chance of being assigned to either group.

If you choose to participate in this study, you will be asked to:

1) **Come for two clinic visits (at study start and 6 months)** at the Fred Hutchinson Cancer Research Center (FHCRC) Prevention Center Clinic located in the Public Health Sciences Building on the FHCRC campus at Southeast Lake Union in Seattle. These clinic visits will include:
    - **A brief physical exam** (blood pressure, height, weight, waist and hip measurements)
    - **A review of current medications**. You will be asked to bring in a detailed list of their current medications and supplements, including drug name, dose, and frequency of use. You will also bring in your medication bottles so that staff may copy the labels to record information.
    - **A blood sample** of 50ml (approximately 3 tablespoons) taken from arm by a trained and certified phlebotomist. The blood will be used to assess level of biomarkers associated with cancer recurrence.

    If you are unable or unwilling to go to the Prevention Center, these visits may be conducted remotely, and we would ask you for the following:

    - **Limited physical data**. We will ask you to weigh yourself at home and report to us. If available, we will record your height from your medical records, and if not, we will ask you to report your height to us. Blood pressure, waist and hip measurements would not be collected.
    - **A review of current medications**. You will be asked to provide a list of prescription and non-prescription medications including drug name, dose, and frequency of use. If you prefer to share via photos, this will be an option.
    - **A blood sample** of up to 50ml (approximately 3 tablespoons) taken from arm by a trained and certified phlebotomist. We will ask you to visit a lab close to your home to have your blood drawn, where it will be shipped to our lab for processing. The blood will be used to assess level of biomarkers associated with cancer recurrence.

2) **Complete a series of questionnaires at home (study start, 3 months, and 6 months)**. These will include detailed questions about the foods you eat, your exercise and health habits, your medical history and health status, and quality of life (social support, thoughts and feelings). You may choose not to answer any question on any questionnaire.

3) **Provide saliva samples (study start and 6 months)**. Saliva collection kits and instructions will be mailed to your home prior to the clinic visits (or at the study start and 6-month time points if you are not being seen in-person). You will be asked to place a collection device in your mouth and provide saliva at bedtime for the 3 nights prior to the study baseline and 6-month time points. You will bring your collected samples with you to your scheduled clinic visit or return via mail using pre-paid postage materials if you are not seen for in-person study visits. A research staff member will contact you prior to collection to remind you of the collection. The saliva samples will be used to assess cortisol levels, a hormone associated with stress.

4) **Provide a 24-hour urine sample (only if you are seen for in-person study visits) study start and 6 months)**. 24-hour urine collection kits and instructions will be mailed to your home prior to the clinic visits. You will be asked to collect all urine for the 24 hours prior to your clinic visit and store it in your refrigerator until you bring it in with you to your clinic visit. A research staff member will contact you prior to collection to remind you of the collection. The urine samples will be used to assess norepinephrine levels, a hormone associated with stress.
If you are unwilling or unable to be seen for in-person visits at the Prevention Center, we will not ask you to provide a urine sample at study start or 6-month time points.

5) **Wear a physical activity monitor (study start and 6 months).** For one week, at the beginning and end of the study, you will wear a physical activity monitor (like a Fitbit) that measures your

physical activity level (duration and intensity). The monitor should be worn throughout the day and at night, except when showering/bathing or swimming.

6) **If you are randomized to the exercise program, you will also:**
   1. Meet with the exercise trainer in-person or virtually for one hour to learn how to safely exercise
   2. Exercise at home, with an ultimate goal of 150 minutes of exercise per week
   3. Have weekly telephone calls with the exercise trainer. The purposes of these calls is to provide support and continuously assess exercise needs and make modifications as needed.
   4. Keep a daily log of physical activity.
   5. Wear a physical activity monitor for one week at a few additional time points (2, 3, and 4 months).

7) **If you are randomized to the waitlist control group:**
   1. You will continue your usual activities.
   2. At the end of 6 months, you will be offered the exercise program, including the in-person or virtual meeting with the exercise trainer and the weekly telephone call support.

8) **Medical Record Review**. We would like to record information from your medical records. We will record information about you like your age and insurance status. We will also record information that doctors record in your medical record including your medical history, information about your cancer, laboratory and imaging tests, medications you are taking, and information about your cancer treatments. If you visited another facility for care related to your cancer prior to this study, you will be asked to provide your consent to release those medical records to the study team.

The table below describes the timeline for research visits and data collection

		Month 0 (study start)	**Month 2**	**Month 3**	**Month 4**	**Month 6**
Clinic Visit (remote or in-person) (with saliva, urine [for in-person visits], and blood collection)	Exercise Group	✓				✓
	Waitlist Group	✓				✓
Questionnaires	Exercise Group	✓		✓		✓
	Waitlist Group	✓		✓		✓
Exercise Training followed by weekly calls	Exercise Group	✓	✓	✓	✓	✓
	Waitlist Group					✓
Daily Physical Activity Log	Exercise Group	✓	✓	✓	✓	✓
	Waitlist Group					✓
Physical Activity Monitor	Exercise Group	✓	✓	✓	✓	✓
	Waitlist Group	✓				✓

RISKS, STRESS, OR DISCOMFORT

The potential risks associated with this study include:

Questionnaires: Answering questions may cause some emotional discomfort. You may choose not to answer one or any of these questions on the questionnaires. If you choose not to answer these questions, it will in no way negatively affect your status as a participant in the study.

Clinic/Lab Visit (physical exam): Collection of height, weight, blood pressure, and hip and waist measurements may be embarrassing to some participants. We will conduct all measurement activities at the FHCRC Prevention Center, and our staff will make every effort to make each participant feel at ease. For those unable or unwilling to come to an in-person visit, we will arrange for you to complete these end-of-study procedures remotely, as described on p. 2 of this consent form.

Exercise Program: The major risks of participating in this monitored program include fatigue, muscle soreness, and possible joint or muscle injury. Some exercise programs have a very small risk of a sudden heart attack. These risks will be reduced through instruction and monitoring from a trained exercise specialist, proper warm-up/cool-down periods, a gradual progression in the length and intensity of the exercise sessions, and avoidance of maximal exertion. The exercise specialist(s) will also teach you techniques to minimize joint and/or muscle injury when you exercise. The exercise specialist will call you weekly to monitor your activity and help ensure safety.

Specimen Collection: There is a small risk of bleeding, bruising, or discomfort at the site of the blood collection. Attention will be taken to apply pressure following the procedure to reduce bleeding. There is also a small risk of fainting or feeling faint during a blood draw. If you begin to feel dizzy or light-headed, you will be asked to lie down for a few minutes until the feeling has passed. There is minimal discomfort associated with collection of other samples (including saliva and urine).

Activity Monitor: Wearing an activity monitor may cause some discomfort. Most people get used to wearing the activity monitor within a short period of time. The monitor will be worn on a belt around the waist and can be worn either over or under clothing.

ALTERNATIVES TO TAKING PART IN THIS STUDY

If you choose not to participate, you and your doctor will discuss the best way to incorporate exercise into your life.

BENEFITS OF THE STUDY

Study participants will benefit from participation in this study by learning how to exercise in a safe and effective way. Participants may also benefit by increasing their fitness level. All study tests and procedures, including blood tests, exercise training, and parking, will be provided to you free of charge. Participants will be actively contributing towards a common goal of identifying lifestyle behaviors that may improve quality of life and may decrease the risk of recurrent ovarian cancer.

SOURCE OF FUNDING

The study team and/or the University of Washington is receiving financial support from the National Cancer Institute.

CONFIDENTIALITY OF RESEARCH INFORMATION

The researchers will keep your study information confidential. We will assign a unique study code to your study information. Information that identifies you will be kept in a secure location. We will destroy any link between you and the study information once the study has ended and after the records retention period required by state and/or federal law. If the results of this study are published, we will not use any information that identifies you.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your study information or research records may be examined. The reviewers will protect your privacy. Your study information or research record will not be used to put you at legal risk of harm.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

We have a Certificate of Confidentiality from the federal National Cancer Institute. This helps us protect your privacy. The Certificate means that we do not have to give out identifying information about you even

if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.
We can't use the Certificate to withhold your research information if you give your written consent to give it to an insurer, employer, or other person. Also, you or a member of your family can share information about yourself or your part in this research if you wish.

There are some limits to this protection. We will voluntarily provide the information to:

- A member of the federal government who needs it in order to audit or evaluate the research;
- Individuals at the University of Washington, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- The federal Food and Drug Administration (FDA), if required by the FDA;
- Local authorities, if we learn of child abuse, elder abuse, or the intent to harm yourself or others.

OTHER INFORMATION

You may refuse to participate and you are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled.

You are responsible for the cost of your clinical care that includes, but is not limited to, follow up visits with your doctor for your cancer or other clinic visits that occur for any reason during the duration of this study. All clinical study components (blood draws, saliva kits, urine collection, and sample processing will be billed directly to the study team.

You will receive a total of $50 for completing the activities related to the study. You will receive $10 for completing the baseline questionnaire and clinic visit (in-person or remote). You will receive $10 for completing the 3-month survey. You will receive $30 for completing the 6-month questionnaire and clinic visit (in-person or remote). You will be compensated with either cash (check) or gift cards.

After the completion of the study, we may contact you to ask if you would be willing to participate in a future studies related to your ovarian cancer and quality of life. Participation in future studies will have a similar consent process, and participation would be optional.

RESEARCH-RELATED INJURY

If you think you have a medical problem or illness related to this research, contact Dr. Kathryn Pennington's office right away at 206-598-8300. They will assess you or refer you for treatment.

The costs of the treatment may be billed to you or your health insurance just like other medical costs, or it may be covered by the UW's discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. You may also call collect to the UW Human Subjects Division at 206-221-5940 if you do not otherwise have access to a telephone. Ask the researcher if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form. We will bill your health insurance for treating problems that result from your ovarian cancer, exercise program or from standard clinical care. If you have no health insurance or your insurance refuses to pay, we will bill you.

WHAT WILL MY INFORMATION AND/OR SAMPLES BE USED FOR?

Your information and samples (blood, saliva, and urine) will be used for the purposes of this study and will also be stored for possible future assays (tests). These tests might give us additional information in the future about the benefits of exercise in ovarian cancer survivors. By agreeing to participate in this study, your information or blood and urine samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information or samples.

During this study, if the researchers learn new information that may be important to your general health or to your disease or condition, they will share that information with you.

WE INVITE YOU TO DONATE TISSUE SAMPLES FOR OTHER RESEARCH

We invite you to donate tissue from prior surgeries and/or from biopsies that occurred before or may occur during the course of this study. If you join this study, you would not have to donate tissue for future research. You would be free to say "yes" or "no". Regular medical care would not change if you say "no".

If you donate tissue, it would be stored in a secure location. If we want to use your tissue for other research or share it with other scientists for research, an ethics review committee (IRB) would review the request. The IRB would decide if we need to ask for your consent to do the research.

The donated tissues would be used only for research. Researchers will not report their results to you or your doctor. The research results will not appear in your medical record. The results would not affect your medical care.

If you donate tissue for research, you could withdraw the donation at any time by calling Dr. Pennington at (206) 543-3669. You would have no penalty for withdrawing the donation, and regular medical care would not change. We could not return donated tissue, but we might be able to destroy the donated tissue. We could not destroy tissue if it is stored or shared without any label saying who donated it. In this case, it could still be used for research.

Read the question and think about your choice. Please check **YES** or **NO**. You may choose not to donate tissue and still participate in this study.

Do you agree to donate previously collected tissue to study cancer? (check one)			
YES ☐	**NO** ☐	Initials:	Date:

Do you agree to donate tissue that might be collected by your treating clinicians in the future (during the study period) to study cancer? (check one)			
YES ☐	**NO** ☐	Initials:	Date:

Printed name of study staff obtaining consent	Signature	Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can contact the University of Washington Human Subjects Division by phone at 206-543-0098 or by email at hsdinfo@uw.edu. Additional, I can contact the Fred Hutchinson Cancer Research Center Institutional Review Office by phone at 206-667-5900 or by email at irodirector@fredhutch.org. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject	Date	Signature of subject

Copies to: Researcher

Subject