OFFICIAL STUDY TITLE: ACTIVATE: A PILOT RANDOMIZED ACTIVITY COACHING TRIAL TO INCREASE VITALITY AND ENERGY DURING POST-OPERATIVE PELVIC RADIATION THERAPY FOR ENDOMETRIAL CANCER

PROTOCOL

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ACTIVATE: A pilot randomized **A**ctivity **C**oaching **T**rial to **I**ncrease **V**it**a**li**t**y and **E**nergy during post-operative pelvic radiation therapy for endometrial cancer

Inova Protocol #:	INOVA-2024-91
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SUMMARY OF CHANGES

Inova Study #: INOVA-2024-91

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Protocol Modification #: 1

REVISION HISTORY

#	Section	Page(s)	Summary of Changes	Consent Change (Y/N)
1.	Table 1.Schedule of study procedures; 9.3	17 and 30	Removed vital signs as a data element for collection and kept only height and weight at enrollment	
2.	9.2;11.1.4	29 and 35	Added option to collect PROs using a paper survey or allow our clinical research coordinators to interview the patient by phone or in-person	
3.	All	1-47	Protocol Version Date was updated from “8/14/2024” to “05/12/2025”	
4.				
5.				

ABSTRACT

The integration of exercise therapy is recommended for cancer patients and survivors to mitigate the side effects of therapy and the risk of recurrence. Cancer patients, however, often experience barriers to meeting the recommended guidelines. It is well documented that at least two-thirds of cancer patients are unable to adhere to the recommendation of exercise due to symptoms and barriers, with women being more likely than men to report barriers to adherence to exercise. Patients with low adherence report higher symptom burden including pain and fatigue. Radiation treatment, with usually a daily treatment schedule, poses additional barriers to engaging in routine exercise and there is a large gap in data to guide the incorporation of exercise therapy into the treatment of patients receiving radiation given these unique challenges. The available data is limited largely to men with prostate cancer, which reports improvement in a number of symptoms with exercise during treatment.

The most common gynecologic malignancy in the United States is endometrial cancer, and the incidence continues to rise. Many women with endometrial cancer will be recommended to undergo pelvic radiation therapy to reduce recurrence risks. For women undergoing pelvic radiation therapy, fatigue-limiting activities of daily living (ADLs) is a common acute side effect of therapy. Although it is accepted that exercise helps treatment-related fatigue in the general cancer population, *patient-specific factors* (more advanced age, post-operative status, and the prevalence of baseline obesity and co-morbidities) and *treatment-specific factors* (daily radiation for 5 weeks, often concurrent chemotherapy) pose significant challenges with the feasibility of endometrial cancer patients to engage in exercise.

This study will explore the feasibility of conducting a randomized trial of a personalized exercise coaching program to encourage physical activity for women undergoing adjuvant pelvic intensity-modulated radiation therapy treatment for endometrial cancer to guide the design of future studies to test the hypothesis that a relationship with an exercise coach will increase adherence to exercise. Such a follow-up study will be suited to investigate the effect of exercise to treat or mitigate fatigue, to identify successful strategies for improving adherence to exercise, and to understand which population of patients may benefit most from a targeted program to increase motivation and overcome barriers to exercise.

In this pilot study, a total of 16 women treated with total or modified radical hysterectomy and surgical staging for Stage I-IVA endometrial cancer who are planned to complete pelvic external beam radiation therapy as part of their adjuvant treatment will be included. The intervention is an exercise coaching program which will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients. The purpose of each check-in is to address readiness for exercise, identify barriers, and develop an individualized plan for exercise for the week with a goal of increasing activity to 150 minutes of moderate activity per week using any form of activity that is enjoyable and accessible to the patient. This will be accomplished by shaping behavior through personalized recommendations. Patients will be randomized to

either an immediate- or delayed-start of their exercise coaching program. Women randomized to the immediate-start group will start the intervention during the first week of radiation therapy and continue through and post-completion of radiation. Women randomized to the delayed-start group will start the intervention at 6-8 weeks post-radiation, a more typical period in survivorship where exercise counseling may begin. Participants will be asked to wear an activity monitor to track steps and moderate activity minutes and to complete assessments of patient-reported cancer-related fatigue, bowel/urinary toxicity, sexual health, and quality of life and participate in a six-minute walk test (6MWT) at predefined time points throughout the study.

The primary objective of this study is to evaluate the feasibility of conducting a randomized trial with an exercise coaching program as the intervention, with the secondary objective to provide initial efficacy on improving treatment-related fatigue, understand the prevalence of baseline fatigue, and explore potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators) for a follow-up study.

ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition of Terms
6MWT	Six-Minute Walk Test
ADLs	Activities of daily living
AE	Adverse Event
ASCO	American Society of Clinical Oncology
BP	Blood pressure
CFR	Code of Federal Regulations
CRF	Cancer-related fatigue
CRP	C reactive protein
DSM	Date Safety and Monitoring
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPIC	Expanded Prostate Cancer Index Composite
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Food and Drug Administration
FFIS	Fatigue functional impact scale
FWA	Federal wide Assurance
Fx	Fraction
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed consent form
ID	Identification
IL-1	Interleukin-1
IMRT	Intensity-modulated radiotherapy
IND	Investigational New Drug
IRB	Institutional Review Board
ISCI	Inova Schar Cancer Institute
MRN	Medical Record Number
NCCN	National Comprehensive Cancer Network
ORI	Office of Research Integrity
PHI	Protected Health Information
PI	Principal Investigator
PR	Patient-Reported Outcomes Measurement Information System
QoL	Quality of Life
RR	Respiratory rate
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
sIL-6R	Systemic interleukin-6 soluble receptor
sTNF-RII	Soluble TNF receptor type II

PROTOCOL SYNOPSIS

Study Title:	ACTIVATE: A pilot randomized **A**ctivity **C**oaching **T**rial to **I**ncrease **V**it**a**li**t**y and **E**nergy during post-operative pelvic radiation therapy for endometrial cancer
Source of Funding:	Inova Schar Cancer Institute
Study Rationale:	The integration of exercise therapy is recommended for cancer patients and survivors to mitigate the side effects of therapy and reduce recurrence risks. Cancer patients, however, often experience barriers to meeting the recommended guidelines. It is well documented that at least two-thirds of cancer patients are unable to adhere to the recommendation of exercise due to symptoms and barriers, with women being more likely than men to report barriers to adherence to exercise. For women undergoing pelvic radiation therapy, fatigue-limiting activities of daily living (ADLs) is a common acute side effect of therapy; however, *patient-specific factors* (more advanced age, post-operative status, and the prevalence of baseline obesity and co-morbidities) and *treatment-specific factors* (daily radiation for 5 weeks, often concurrent chemotherapy) pose significant challenges with the feasibility of endometrial cancer patients to engage in exercise. Despite the known benefits of exercise, there is a notable lack of data on how to effectively integrate exercise into the treatment regimens of women receiving pelvic radiation therapy. Most existing studies focus on other cancer types or on male patients, leaving a significant gap in the literature regarding female patients with gynecological malignancies. In this pilot study, a total of 16 women treated with total or modified radical hysterectomy and surgical staging for Stage I-IVA endometrial cancer who are planned to complete pelvic external beam radiation therapy as part of their adjuvant treatment will be included. The intervention is an exercise coaching program which will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients. The

	purpose of each check-in is to address readiness for exercise, identify barriers, and develop an individualized plan for exercise for the week with a goal of increasing activity to 150 minutes of moderate activity per week using any form of activity that is enjoyable and accessible to the patient. This will be accomplished by shaping behavior through personalized recommendations. Patients will be randomized to either an immediate- or delayed-start of their exercise coaching program. Women randomized to the immediate-start group will start the intervention during the first week of radiation therapy and continue through and post-completion of radiation. Women randomized to the delayed-start group will start the intervention at 6-8 weeks post-radiation, a more typical period in survivorship where exercise counseling may begin. Participants will be asked to wear an activity monitor to track steps and moderate activity minutes and to complete assessments of patient-reported cancer-related fatigue, bowel/urinary toxicity, sexual health, and quality of life and participate in a six-minute walk test (6MWT) at predefined time points throughout the study. The primary objective of this study is to evaluate the feasibility of conducting a randomized trial with an exercise coaching program as the intervention, with the secondary objective to provide initial efficacy on improving treatment-related fatigue, understand the prevalence of baseline fatigue, and explore potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators) for a follow-up study.
Study Objective(s):	Primary: The primary objective of this study is to evaluate the feasibility of conducting a randomized trial of an exercise coaching program to encourage physical activity for women treated with adjuvant pelvic intensity-modulated radiation therapy treatment for endometrial cancer. Secondary: 1) To collect initial efficacy evaluation of the exercise coaching program on patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as

	well as distance walked during 6MWT between the immediate and delayed-start group from baseline to pre-specified time points (end of RT, 5-7 weeks post RT, and 16-19 weeks post RT) to guide statistical planning for follow-up study. 2) To measure the prevalence of fatigue at baseline in the population of endometrial cancer patients recommended pelvic radiation therapy using data collected in the screening process. 3) To explore potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators).
Test Product(s)/Agent(s):	The exercise coaching program will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients.
Study Design:	Pilot feasibility study using randomization of immediate versus delayed intervention.
Participant Population Key Criteria for Inclusion and Exclusion:	<u>Inclusion Criteria:</u> • At least 18 years of age • Pathologic diagnosis of endometrial cancer (any histology, Stage I-IVA) • Has undergone modified radical or radical hysterectomy • Plan to receive adjuvant treatment with pelvic external beam radiation therapy at ISCI • ECOG performance status of 0-1 • Patient has a computer, smart phone, or tablet for virtual access to the web-based platform and email • Able to read, understand and provide written informed consent • Deemed appropriate for unmonitored exercise by treating physician based on the following evidence-based criteria (1) o Walk without any assistance or assistance device o Absence of significant cognitive impairment o Absence of high risk for falls • Participant does not need to refrain from any activity <u>Exclusion Criteria:</u> • Unable to schedule and attend coaching visits

	• Participation in a regular exercise program of ≥150 minutes of moderate intensity exercise a week at baseline
	• Unable to perform the five-times stand test
	• Medical comorbidities including:
	  o Unstable angina
	  o Uncontrolled dysrhythmias
	  o Acute pulmonary embolus
	  o Active pulmonary infection

Number of Participants:	16 participants randomized 1:1 to immediate start or delayed start intervention Stratification will be performed to divide the number of patients with no to mild fatigue (0-3 numeric rating scale) from patients with moderate to severe fatigue (4-10) because it is possible that the intervention effect is variable depending on baseline level of fatigue.
Study Duration:	Each participant's participation will last up to 6 months.
Study Phases: Screening Study Treatment Follow-Up	Screening for eligibility and obtaining consent The exercise coaching program will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients with a goal of increasing activity to 150 minutes of moderate activity per week. This will be accomplished by shaping behavior through personalized recommendations. Women randomized to the immediate start group will start the intervention during the first week of radiation therapy and continue through and post-completion of radiation. Women randomized to the delayed start group will start the intervention at 6-8 weeks post-radiation. Steps, active minutes, patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as well as distance walked during 6MWT.

Efficacy Evaluations:	Steps, active minutes, and heart rate measured by a Fitbit device PROMIS Short Form v1.0 – Fatigue 13a (FACIT-Fatigue) EPIC Prostate Bowel and Bladder assessment (short form) PROMIS-29 Profile v2.1 QoL (physical function, anxiety, depression, sleep disturbance, pain interference/intensity, ability to participate in social roles and activities) PROMIS Short Form v2.0 – Cognitive Function 4a PROMIS Sexual Function and Satisfaction v2.0 Brief Profile (Female) PROMIS Short Form v1.0 – Self-Efficacy for Chronic Conditions – Managing Daily Activities 4a and Managing Symptoms 4a 6MWT
Safety Evaluations:	Patients can communicate any concerns or safety issues during their weekly check-ins with the exercise coach. They will also be provided with information for contacting an on-call doctor as part of usual care to report any concerning symptoms should they occur outside of the standard evaluation schedule.
Statistical and Analytical Plan:	This study will enroll 16 patients. At the Inova Schar Cancer Institute Fairfax location, approximately 24 patients will undergo a course of pelvic radiation per year. Additionally, approximately 24 patients will undergo a course of pelvic radiation per year across Inova Loudoun, Inova Alexandria, and Inova Fair Oaks Hospitals. With the goal of the study to evaluate adherence to and the acceptability and feasibility of the intervention as part of a pilot study, the sample size was determined with the goal to complete accrual of the study within 1 year, accruing across

	all 4 sites. <u>Primary Objective Analytical Plan</u> Feasibility of conducting a randomized trial of this nature will be evaluated on the basis of process feasibility and resources and data-management feasibility. The *process* feasibility will be evaluated on: 1. Recruitment acceptability from the provider and patient perspective: a. Provider acceptability of the intervention will be defined as the proportion of patients identified on pre-screening by the PI that the primary clinician agrees of patient suitability for offering enrollment on the trial and proceeding to completion of screening steps if patient is interested in the study. We set an a priori goal of 50% provider acceptability. b. Patient acceptability of the intervention will be defined as the proportion of patients who agreed to consent and then proceed to completion of screening steps. We set an a priori goal of 50% patient acceptability. 2. Appropriateness of the screening criteria: a. Screening criteria appropriateness will be defined as the proportion of patients who are screened who proceeded to allocation of intervention groups. We set an a priori goal of 50% of appropriateness of the screening criteria. 3. Adherence to the exercise coaching session intervention: a. Individual adherence to coaching sessions will be defined as complete adherence when engaging in 10 of the 10 planned exercise coaching sessions and high adherence as engaging in at least 7 of the planned 10 exercise coach check-ins. We set an a priori goal of overall 70% participant adherence to the coaching sessions, to be analyzed per cohort (6 of 8 participants in each arm demonstrating high adherence as defined above). 4. Adherence to the physical activity monitor usage to

	track steps and active minutes: a. Individual adherence to the physical activity monitor will be defined as wearing the activity tracker for at least 8 hours a day for 70% of the days in the study. Heart rate will be used to determine wear-time. We set an a priori goal of overall 70% participant adherence to the physical activity monitor, to be analyzed per cohort (6 of 8 participants in each arm demonstrating adherence as defined above). 5. Adherence to recommendation of 150 minutes per week of moderate physical activity: a. Individual adherence to regular physical activity will be defined as meeting the recommendation of 150 minutes of moderate physical activity per week, based on the Physical Activity Guidelines for Americans developed by the U.S. Department of Health and Human Services (HHS). The target for participant adherence is set at an a priori goal of 70%. The *resource and management* feasibility will be assessed based on the capacity of the exercise coach and research team to perform the required tasks of the protocol: 1. Adherence to the timeline of study procedures and human and data management issues that could potentially arise during a full-scale RCT will be tracked. Adherence to the study timeline for completion of required patient surveys and 6MWT as well as appropriate scheduling (patient attendance not required) of the exercise coaching sessions and follow-ups will be a proxy measurement of research resource and human data management acceptability. We set an a priori goal of 80% adherence. <u>Secondary Objective Analytical Plan</u> 1. Changes in patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as well as distance walked during 6MWT from baseline to pre-specified time points (end of RT, 5-7 weeks post RT, and 16-19 weeks post RT) within and between each group will be

	compared using two-sample t-test or Wilcoxon Rank Sum test when appropriate. Repeated measure models/linear mixed effect models may also be used to explore the changes in self-reported questionnaires over time among different treatment groups. Data will be analyzed based on the intention-to-treat principle and used to estimate treatment effect size for future trial design. 2. Prevalence of fatigue at baseline in the population of endometrial cancer patients receiving pelvic radiation therapy will be reported using data collected in the screening process. 3. Exploratory analysis of potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators) will be performed.
Data and Safety Monitoring Plan:	Internal quality assurance team will be responsible for monitoring the safety and data acquisition for this study.

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TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Enrollment[1]	RT Simulation	Radiation					Post-Radiation		
Week Number	0		1	(Fraction 1-5)	(Fraction 6-10)	(Fraction 11-15)	(Fraction 16-20)	(Fraction 21-25)	5-7 weeks post RT follow-up[2]	6-8 weeks post RT	16-19 weeks post RT follow-up[3]
ALL PATIENTS											
Informed Consent	X										
Review Inclusion/Exclusion Criteria	X										
Fatigue 0-10 Numeric Rating Scale	X										
Height and weight		X									
Randomization		X									
Patient-reported demographics/medical history (comorbidities)		X									
Stages of change metric		X						X	X		X
Patient-reported fatigue (FACIT-Fatigue)		X						X	X		X
Patient-reported toxicity (EPIC bowel and urinary short form assessments)		X						X	X		X
PROMIS-29 Profile v2.1 QoL		X						X	X		X
PROMIS Cognitive Function		X						X	X		X
PROMIS Self-Efficacy for Chronic Conditions		X						X	X		X

(Continued) TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Enrollment[1]	RT Simulation	Radiation					Post-Radiation		
Week Number	0		1	(Fraction 1-5)	(Fraction 6-10)	(Fraction 11-15)	(Fraction 16-20)	(Fraction 21-25)	5-7 weeks post RT follow-up[2]	6-8 weeks post RT	16-19 weeks post RT follow-up[3]
6-Minute Walk Test (6MWT)		X						X	X		X
Weekly Active Minute, step and heart rate data collection from Fitbit			X-Active minute, step, and heart rate data collected from time of simulation to last f/u (16-19 weeks post RT) for all patients								
PROMIS Brief Profile Sexual Function and Satisfaction									X		X
Pelvic radiation therapy with IMRT				X	X	X	X	X			
Satisfaction survey											X
Recorded semi-structured exit interview with study PI											X
Early-Intervention Group											
Weekly exercise coach check-ins start x 10 weeks				X (Patients start first check-in during first 5 fractions of RT and continue for a total of 10 weekly sessions. With this schedule, the final session will be post-pelvic RT completion)							
5-10 minute bi-weekly Fitbit check-in call										X (Once every 2 weeks, starting the week after coaching sessions complete for 10 weeks (total 5 calls).	
Delayed-Intervention Group											
Weekly exercise coach check-ins start x 10 weeks										X (Patients start first check-in after 5–7-week post RT follow-	

(Continued) TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	Screening	Enrollment[1]	RT Simulation	Radiation					Post-Radiation		
Week Number	0		1	(Fraction 1-5)	(Fraction 6-10)	(Fraction 11-15)	(Fraction 16-20)	(Fraction 21-25)	5-7 weeks post RT follow-up[2]	6-8 weeks post RT	16-19 weeks post RT follow-up[3]
										up, starting 6-8 weeks post RT, and continue for a total of 10 sessions)	
5-10 minute bi-weekly Fitbit check-in call				X (Once every 2 weeks starting the first week of RT for a total of 10 weeks (total 5 calls)							

[1]Enrollment would occur any time within 7days (before or after) simulation, prior to the start of radiation.

[2]5-7 week post RT follow-up intended to be soon after completion of intervention in the early-intervention group and before intervention in the delayed-intervention group for purposes of assessment.

[3]16-19 week post RT follow-up intended to be soon after completion of intervention in the delayed-intervention group for purposes of assessment collection.

1. BACKGROUND

Cancer-related fatigue (CRF) is a significant and distressing symptom for women undergoing pelvic radiation therapy for endometrial cancer, often severely limiting their ability to engage in daily activities and reducing their overall quality of life (QoL) (2). Although exercise has been shown to be an effective intervention for mitigating CRF in various cancer populations, women with gynecological malignancies, particularly those undergoing pelvic radiation, face unique barriers that make adherence to exercise challenging. These barriers include advanced age, post-surgical recovery, baseline obesity, and the demanding nature of radiation treatments, which are often compounded by concurrent chemotherapy (3-9). Additionally, environmental and social factors, such as lack of access to exercise facilities and limited support from healthcare providers or family, further discourage regular physical activity (10).

Introducing a personalized exercise coaching program offers a promising strategy to overcome these barriers and improve adherence to exercise during treatment (3-9). By providing tailored exercise plans and continuous support through regular coaching sessions, this approach aims to empower patients to incorporate physical activity into their routine despite the challenges posed by their treatment and personal circumstances. Improved adherence to exercise not only has the potential to better manage CRF but also addresses other symptoms associated with cancer and its treatment, such as pain, urinary and bowel dysfunction, and reduced QoL (11-13). By enhancing adherence through personalized coaching, patients may experience more effective symptom management, leading to improved health outcomes and overall well-being during and after their cancer treatment (14, 15). However, none of the available literature focuses on women undergoing pelvic radiation therapy.

1.1 Study Disease(s) or Condition(s)

1.1.1 Epidemiology of the Disease

Nearly 68,000 women will be diagnosed with endometrial cancer in the US in 2024 (22). Also commonly called uterine cancer, endometrial cancer is the most frequently diagnosed gynecologic cancer and the fourth most diagnosed cancer in women, with a median age of diagnosis of 62 years. While the exact cause is unknown, endometrial cancer's incidence and death rate have increased over the years, possibly due to factors such as obesity and hormone replacement therapy to manage other medical conditions (23).

1.2 Product(s) / Agent(s)

Not applicable.

1.3 Rationale

Cancer-related fatigue (CRF) is a common and distressing symptom experienced by cancer patients, particularly those undergoing pelvic radiation therapy for endometrial cancer. As the most prevalent gynecologic malignancy in the United States, endometrial cancer has seen a rising incidence driven by factors such as

obesity and hormone replacement therapy. To reduce the risk of recurrence, many women with this diagnosis undergo pelvic radiation therapy to lower recurrence risks. However, CRF is a common acute side effect of this treatment, significantly limiting activities of daily living (ADLs). Although the exact prevalence of CRF in women with endometrial cancer undergoing pelvic radiation therapy is not well documented, studies suggest that CRF affects up to 93% of this patient population (24, 25), severely impacting their QoL and ability to adhere to treatment protocols.

An increasing body of evidence supports using exercise as an effective intervention for managing CRF. Several systematic reviews and meta-analyses have demonstrated that exercise, including aerobic and resistance training, can significantly reduce the severity of fatigue during and after cancer treatment (19-21). The ASCO-Society for Integrative Oncology guidelines strongly recommend exercise as a therapeutic strategy for CRF, advising that exercise regimens be tailored to each patient's capabilities (26, 27). Despite this broad endorsement, the underlying mechanisms by which exercise mitigates CRF are not fully understood, and most existing studies have focused on other cancer types. There is limited research addressing the unique needs of women with endometrial cancer undergoing pelvic radiation therapy (28-30).

Women with endometrial cancer undergoing pelvic radiation therapy face numerous barriers to regular physical activity, including older age, post-surgical recovery challenges, baseline obesity, and comorbidities. The demanding nature of daily radiation treatments, which often extend over several weeks and may be combined with chemotherapy, further complicates their ability to engage in exercise. Additionally, social and environmental factors, such as lack of encouragement from family and friends, limited access to safe exercise environments, and financial constraints, further reduce adherence to exercise recommendations, exacerbating CRF and other treatment-related symptoms (10).

A web-based personalized exercise coaching program offers an innovative solution to help these patients overcome the barriers to physical activity, including those related to recovery, fatigue, and logistical challenges. Emerging evidence (3-9) suggests that these programs can effectively address these obstacles by offering tailored exercise plans, continuous support, and motivation, thereby improving adherence to recommended physical activity regimens during and after cancer treatment.

Given the prevalence of CRF and its significant impact on patients' QoL, interventions aimed at reducing fatigue are vital.

The ACTIVATE trial is designed to evaluate the feasibility and potential efficacy of a personalized, web-based exercise coaching program for women undergoing postoperative pelvic radiation therapy for endometrial cancer. This study aims to overcome the barriers to physical activity by providing tailored exercise plans and continuous support through certified exercise coaches. Recognizing that recruitment through healthcare professionals leads to higher recruitment rates (31), radiation oncologists will recruit endometrial cancer patients directly from their practices.

The primary objective of the ACTIVATE trial is to evaluate the feasibility of conducting a randomized trial of this nature, focusing on adherence to the exercise coaching program and the acceptability of the intervention among participants and providers. Given the significant barriers faced by this patient population, this objective is crucial to determine whether such an intervention can be successfully implemented in a real-world clinical setting.

Secondary objectives include evaluating the initial efficacy of the exercise coaching program on patient-reported outcomes such as fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function, satisfaction, self-efficacy, and participation in the six-minute walk test (6MWT). The study will measure the prevalence of baseline fatigue in this population, identify potential mediators (e.g., improvements in sleep (32, 33), pain (34, 35), depression (34, 36)) and moderators (e.g., baseline fatigue severity, readiness to change) of the intervention's effects, and provide data to support the design of a future randomized controlled trial.

By capturing both patient-reported measures and functional measures of fatigue (e.g., 6MWT), we aim to design studies to provide supportive data that could, in the future, inform healthcare payors for the reimbursement of exercise coaching personnel and programs for patients undergoing radiation treatments for cancer as a means of improving patient QoL and overall outcomes.

1.4 Relevant Literature and Data

CRF is a common symptom in patients with cancer and is experienced by 80% of individuals receiving cancer therapy (2). Due to the prevalence and QoL influence that fatigue has on these patients, it is important to assess interventions that aim to reduce the impact of fatigue. Several systematic reviews explore the evidence supporting exercise as a treatment for CRF, with interest growing over the past five years (19-21). However, none of the available literature focuses on women undergoing pelvic radiation therapy (28-30), where CRF can affect up to 93% of this patient group (24, 25). For women undergoing pelvic radiation therapy for gynecological malignancies, fatigue limiting ADLs is a common acute side effect of therapy with no known mitigation recommendations (16).

The cause of fatigue in patients with cancer is often multi-factorial and can be related to clinical, psychological, and behavioral factors. Potential contributing aspects include medical comorbidities, medications, nutritional issues, and psychological and physical symptoms (38). Inflammation may also be involved in the etiology of CRF. Researchers have proposed that tumors and the therapies used to remove them can activate the pro-inflammatory cytokine network, leading to fatigue symptoms through cytokine signaling in the body’s central nervous system (39).

Various cytokines and inflammatory markers have been correlated to predict fatigue in cancer patients. A study of breast cancer patients receiving adjuvant radiation showed that localized irradiation encourages increased systemic interleukin-6 soluble receptor (sIL-6R) during treatment in those who reported elevated levels of fatigue before, during, and after treatment (40). Another study of patients undergoing radiation therapy for early-stage breast or prostate cancer found

that increased serum levels of inflammatory markers C reactive protein (CRP) and IL-1 receptor antagonist were associated with increased fatigue (41). Approximately 20-30% of cancer survivors report persistent fatigue for years after treatment, correlated with elevated circulating markers of inflammation, such as TNF receptor type II (sTNF-RII) (42,43). Studies have also reported associations between CRF and variations in the immune and neuroendocrine system, including changes in leukocyte subsets, reactivation of latent herpesviruses, dysregulated cortisol levels, reduced glucocorticoid receptor sensitivity, and autonomic nervous system changes (38).

Multiple observational studies report that exercise is associated with reduced risk of recurrence and mortality, and the integration of exercise therapy is recommended by NCCN and ASCO for cancer patients and survivors to reduce the relapse risk and mitigate the side effects of therapy, including fatigue (14,21,37). However, there is a lack of data to guide the incorporation of exercise therapy into treating patients receiving radiation therapy. The available data is largely limited to incorporating exercise in the radiation treatment of men with prostate cancer, which reports improvement in physical function domains and the potential for increased radiotherapy effectiveness (12,13). Reduction of fatigue in patients with both prostate and breast cancer receiving radiation has been reported as a result of exercise (11,14).

The American College of Sports Medicine recommends that cancer patients and survivors participate in at least 150 minutes of moderate-intensity activity each week (44). Various aerobic exercise regimens have been shown to benefit fatigue, ranging from home-based programs to supervised, laboratory-based programs (44,45). However, there is inconsistent data regarding the effect of resistance exercise in this patient population and strategic supportive programs or personnel to support patients in accomplishing the recommended guidelines for activity (21,46).

Previously, there was some concern that exercise during therapy could worsen fatigue or worsen side effects; however, in the recently published ASCO guidelines on exercise, diet, and weight management during cancer treatment, an expert panel performed a systematic review of the medical literature leading to a recommendation for oncology providers to recommend aerobic and resistance exercise during active treatment with curative intent to mitigate side effects of cancer treatment based on data suggesting exercise interventions during active treatment reduce fatigue, preserve cardiorespiratory fitness, physical functioning and strength and in some populations improve QoL and reduce anxiety and depression. Furthermore, the guidelines outline that exercise intervention during treatment has a low risk of adverse events (37). The ASCO-Society for Integrative Oncology guidelines strongly recommend exercise as a therapeutic strategy for CRF, advising that exercise regimens be tailored to each patient's capabilities (26, 27). Therefore, exercise during treatment should be encouraged, and it is important that the magnitude of benefit be quantified to support ongoing efforts to integrate exercise during treatment and reduce barriers to exercise for patients.

Studies have shown that a web-based personalized exercise coaching program can effectively address many barriers cancer patients face when trying to engage in

regular physical activity. These barriers often include limited access to exercise facilities, lack of time, and the need for programs tailored to individual health conditions and preferences. For instance, a study on the remote inclusion of vulnerable users in mHealth intervention design found that web-based health programs effectively reduce barriers to participation, offering flexibility and accessibility that facilitate user engagement, even in populations with limited resources and mobility (47). Similarly, a study demonstrates that personalized web-based health interventions, such as weight loss coaching, can effectively reduce barriers to participation by offering flexibility and accessibility, which are crucial for engaging users with diverse needs and limitations **(7)**. The integration of personalized coaching elements, such as tailored exercise plans and regular feedback, further enhances the effectiveness of these programs by ensuring that the exercise regimens are specifically designed to meet each patient's unique needs and capabilities.

1.5 Compliance Statement

This study will be conducted in full accordance with all applicable Inova Health System's Federalwide Assurance (FWA), Research Policies and Procedures, and all applicable Federal and State laws. These regulations include, but are not limited to, 45 CFR 46 and Good Clinical Practice (GCP).

The investigators will perform the study in accordance with this protocol, will obtain consent using the IRB-approved informed consent form (Appendix 1), and will report unanticipated problems involving risk to participants or others and potential serious or continuing non-compliance in accordance with the Inova Health System's Office of Research Policies and Procedures and all federal requirements. Data collection, recording, and reporting will be accurate and ensure the privacy, health, and welfare of research participants during and after the study.

2. OBJECTIVES

Primary Objective

- The primary objective of this study is to evaluate the feasibility of conducting a randomized trial of an exercise coaching program to encourage physical activity for women treated with adjuvant pelvic intensity-modulated radiation therapy treatment for endometrial cancer.

2.1 Secondary Objective

- To collect initial efficacy evaluation of the exercise coaching program on patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as well as distance walked during 6MWT between the immediate and delayed-start group from baseline to pre-specified time points (end of RT, 5-7 weeks post-RT, and 16-19 weeks post-RT) to guide statistical planning for follow-up study.
- To measure the prevalence of fatigue at baseline in the population of

endometrial cancer patients who are recommended pelvic radiation therapy, using data collected in the screening process (Appendix 2).
- To explore potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators).

3. SETTINGS

3.1 Study Sites

The following investigative sites will be conducting this study:

Inova Alexandria Hospital	Inova Fair Oaks Hospital
4320 Seminary Rd.	3600 Joseph Siewick Dr.
Alexandria, VA 22304	Fairfax, VA 22033
Inova Loudoun Hospital	Inova Center for Personalized Health
44045 Riverside Pkwy.	8100 Innovation Park Dr.
Leesburg, VA 20176	Fairfax, VA 22031

3.2 Community Involvement

A patient advocate will be invited to partner with the research team to provide insights to ensure that the study remains focused on patient needs and perspectives throughout its implementation by (1) helping to identify potential issues related to patient safety, consent, or privacy, (2) suggesting adjustments to make the study more comfortable or less burdensome, (3) ensuring that communication with study participants is clear, respectful, and responsive, and (4) helping to plan and implement follow-up activities, such as communicating results and designing future research studies based on current learnings.

3.3 Outside of Organization

Not applicable.

4. RESOURCES AVAILABLE

4.1 Conducting Research

The Inova Schar Cancer Institute is uniquely suited to be successful at an integrative exercise oncology and radiation therapy study. We anticipate needing up to 12 months to recruit 16 patients for the study. At the Inova Schar Cancer Institute Fairfax location, approximately 24 patients will undergo a course of pelvic radiation per year.

Additionally, approximately 24 patients will undergo a course of pelvic radiation per year across Inova Loudoun, Inova Alexandria, and Inova Fair Oaks Hospitals. With the goal of the study to evaluate adherence to and the acceptability and feasibility of the intervention as part of a pilot study, the sample size was determined with the goal of completing accrual of the study within one year,

accruing across all four sites.

One dedicated day each week will be devoted to identifying possible patients who are eligible and monitoring upcoming survey time points each week by the study PI and team. The research team will be assigned to survey gathering at specified time points.

4.2 Medical Resources

The physicians from the clinics are the medical resources for the subjects.

5. INVESTIGATIONAL PLAN

5.1 General Schema of Study Design

This is a pilot feasibility study using a randomization of immediate versus delayed intervention.

See Table 1: Schedule of Study Procedures.

5.1.1 Hypothesis: This is a pilot study, so there is no hypothesis. However, we have set a priori criteria for evaluating the primary outcomes of the study. This study will explore the feasibility of conducting a randomized trial of an exercise coaching program to encourage physical activity for women undergoing adjuvant pelvic intensity-modulated radiation therapy treatment for endometrial cancer to guide the design of future studies to investigate the effect of exercise to treat or mitigate fatigue, to identify successful strategies for improving adherence to exercise, and to understand which population of patients may benefit most from a targeted program to increase motivation and overcome barriers to exercise.

5.1.2 Study Design: A total of 16 women treated with radical or modified radical hysterectomy for Stage I-IVA endometrial cancer who are planned to complete pelvic external beam radiation therapy as part of their adjuvant treatment will be included. Patients will be randomized to either an immediate- or delayed-start of their exercise coaching program. Women randomized to the immediate-start group will start the intervention during the first week of radiation therapy and continue through and post-completion of radiation. Women randomized to the delayed-start group will start the intervention at 6-8 weeks post-radiation, a more typical period in survivorship where exercise counseling may begin. Participants will be asked to wear an activity monitor to track steps and moderate activity minutes and to complete assessments of patient-reported cancer-related fatigue, bowel/urinary toxicity, sexual health, and quality of life and participate in a six-minute walk test (6MWT) at predefined time points throughout the study.

5.1.3 Study Treatment

The intervention is an exercise coaching program which will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients. The purpose of each check-in is to address readiness for exercise, identify barriers, and develop an individualized plan for exercise for the week with a goal of increasing activity to 150 minutes of moderate activity per week using any form of activity that is enjoyable and accessible to the patient. This will be accomplished by shaping behavior through personalized recommendations. The coach will review Fitbit data, reinforce motivation and adherence, provide tailored suggestions to increase activity, and address barriers to achieving 150 minutes per week of moderate activity. The coach may use MedBridge to create and customize a home exercise program using a vast library of exercise videos and instructions. These can be personalized to meet each patient's specific needs and can be easily shared through the MedBridge platform. MedBridge is HIPAA compliant ensuring patient information is protected and secure. If a participant misses their coaching session, the exercise coach will work with the participant to reschedule within the week and document in EMR. If the coach is unable to reach the participant by phone, a follow up email will also be sent and documented in EMR.

5.2 Product(s) / Agent(s)

Not applicable.

5.3 Allocation to Treatment Groups and Blinding/Randomization

Included subjects were randomly assigned in a 1:1 manner, stratified by baseline fatigue level, using computer-generated numbers. The PI and treating MD will be blinded to the randomization scheme; however, the ultimate allocation to the intervention will not be blinded.

6. STUDY TIMELINE

6.1 Individual Participation

The study duration per participant will be up to six months. Patients will be requested to wear their Fitbit from the start of enrollment to the 16-19 weeks post RT visit, participating in standard-of-care weekly visits during RT at 5-7 weeks post RT, and again 16-19 weeks post RT. The ten consecutive weekly exercise coaching check-in sessions will start for the early intervention during the first week of RT and the delayed intervention at 6-8 weeks post RT.

6.2 Study Timeline

6.2.1 Treatment intervention

The exercise coaching program will consist of weekly check-ins for ten weeks with a certified exercise coach with expertise in caring for oncology patients with the goal of increasing activity to 150 minutes of moderate

activity per week by shaping behavior through personalized recommendations.

6.2.2 Follow-up

Follow-up will continue for up to 19 weeks after completion of pelvic RT.

7. PARTICIPANT SELECTION

7.1 Eligibility Criteria

Inclusion Criteria:

- At least 18 years of age
- Pathologic diagnosis of endometrial cancer (any histology, Stage I-IVA)
- Has undergone modified radical or radical hysterectomy
- Plan to receive adjuvant treatment with pelvic external beam radiation therapy at ISCI
- ECOG performance status of 0-1
- Patient has a computer, smart phone, or tablet for virtual access to the web-based platform and email
- Able to read, understand and provide written informed consent
- Deemed appropriate for unmonitored exercise by treating physician based on the following evidence-based criteria (1)
    - Walk without any assistance or assistance device
    - Absence of significant cognitive impairment
    - Absence of high risk for falls
- Participant does not need to refrain from any activity

Exclusion Criteria:

- Unable to schedule and attend coaching visits
- Participation in a regular exercise program of ≥150 minutes of moderate intensity exercise a week at baseline
- Unable to perform the five-times stand test
- Medical comorbidities including:
    - Unstable angina
    - Uncontrolled dysrhythmias
    - Acute pulmonary embolus
    - Active pulmonary infection

8. RECRUITMENT METHODS

8.1 Methods

8.1.1 Recruitment

Eligible patients will be pre-screened by PI on a weekly basis, who will then email the primary radiation oncologist. The primary radiation oncologist will determine if the intervention is acceptable to offer to the

potential patient at the time of consultation, and this will inform the provider acceptability ratio, one of the primary outcomes of the study. The primary radiation oncologist will discuss the study with the patient at the time of consultation and, if the patient is interested, will notify the research team to facilitate consent for enrollment.

8.1.2 Screening

Participants will be screened to review inclusion and exclusion criteria (see Appendix 2).

8.1.2.1 Screen Failures

Screen failures are defined as participants who consent to participate in the study but are not subsequently entered into the study. Individuals who do not meet the criteria for participation in this trial (screen failure) cannot be rescreened due to the timeline of intervention with respect to the radiation therapy.

8.1.3 Projected Participants

Recruitment will stop when 16 participants have completed the study.

8.2 Materials

8.2.1 Flyer

During clinic visits, the provider or research staff can introduce the study to participants and hand them a flyer (Appendix 3). Flyers may also be placed within the clinic, such as waiting rooms, reception desks, bulletin boards, and examination rooms. The flyer will include a brief description of the study, eligibility criteria, what participation involves, potential benefits, and risk, as well as contact details for more information.

8.2.2 Social Media

Not applicable.

9. STUDY PROCEDURES

9.1 Screening Visit

9.1.1 Informed Consent/Assent/HIPAA Authorization (Appendix 4)

The Informed Consent Process will take place at screening.

9.1.2 Review of Inclusion/Exclusion Criteria, Demographics and Medical History

9.1.3 Fatigue 0-10 Numeric Rating Scale

9.2 Participant Survey of Patient-Reported Outcomes and Information

All patient-reported outcomes and information (Appendix 5) will be collected using the web-based survey platform REDCap unless the participant prefers paper surveys, in which case paper surveys will be provided. Alternatively, a clinical

research coordinator may conduct the survey by interview either by phone or in person, based on participant preference. Web-based surveys can be completed on a tablet in the clinic or at home, with automatic email reminders sent through REDCap or by the research coordinator (see Appendices 5 and 6). Reminders will be sent 1 and 2 days after the initial survey invitation and 1 day before the survey window closes. The research coordinator may also reach out to participants by phone to remind them to complete the survey and provide verbal assistance as needed.

9.3 Study Intervention Visits

9.3.1 Enrollment

Enrollment would occur any time within 7 days (before or after) simulation, prior to the start of radiation. Items to be completed at enrollment:

- Randomization

9.3.1.1 Height and weight

9.3.1.2 Patient-reported demographics/medical history (comorbidities)

- Stages of change metric
- All patients will be provided with a Fitbit device and provided detailed instructions on its use (Appendix 7). Data monitoring will start with the time that the Fitbit is provided to the patient after consents are signed and will continue to the end of study enrollment.
- The following baseline assessments are collected:
    - FACIT-F
    - EPIC Bowel and Urinary short form assessments
    - PROMIS-29 QoL Metric
    - PROMIS Cognitive Function
    - PROMIS Self-Efficacy for Chronic Conditions
    - 6MWT

9.3.2 RT Simulation

Items to be completed at RT Simulation:

- Fitbit data will be collected on all patients.

9.3.3 Week 1-4 of pelvic RT (Fraction 1-20)

Items to be completed at weeks 1-4 of RT:

- Fitbit data will be collected on all patients.

9.3.4 Week 5 of pelvic RT (Fraction 21-25)

Items to be completed at week 5 of RT:

- Fitbit data will be collected on all patients.
- The following assessments are collected:

  - FACIT-F
  - EPIC Bowel and Urinary short form assessments
  - PROMIS-29 QoL metric
  - PROMIS Cognitive Function
  - PROMIS Self-Efficacy for Chronic Conditions
  - 6MWT

9.3.5 Week 5-7 Post-pelvic RT

Items to be completed at week 5-7 post RT:

- Fitbit data will be collected on all patients.
- The following assessments are collected:
  - FACIT-F
  - EPIC Bowel and Urinary short form assessments
  - PROMIS-29 QoL metric
  - PROMIS Cognitive Function
  - PROMIS Self-Efficacy for Chronic Conditions
  - 6MWT
  - PROMIS Brief Profile Sexual Function and Satisfaction (Female)

9.3.6 Week 16-19 Post-pelvic RT

Items to be completed at week 16-19 post-pelvic RT:

- Fitbit data will be collected on all patients.
- The following assessments are collected:
  - FACIT-F
  - EPIC Bowel and Urinary short form assessments
  - PROMIS-29 QoL metric
  - PROMIS Cognitive Function
  - PROMIS Self-Efficacy for Chronic Conditions
  - 6MWT
  - PROMIS Brief Profile Sexual Function and Satisfaction (Female)
- Satisfaction survey
- Recorded semi-structured exit interview with research PI (Appendix 8)

9.3.7 Weekly Exercise coach check-ins x 10 weeks

- Early intervention cohort: Check-in #1 (60 minutes) to occur during the first week of RT (Fx 1-5). Check-in #2-10 (30 minutes) will continue weekly starting Fx 6-10, and continue through the completion of RT and post-RT for a total of 10 sessions.
- Delayed intervention cohort: Check-in #1 (60 minutes) to occur after the 5-7 week follow-up starting 6-8 weeks after pelvic-RT. Check-in #2-10 (30 minutes) will continue weekly a total of 10 sessions.

9.3.8 Bi-weekly active attention control check-ins x 10 weeks

- Early intervention cohort: Check-ins, once every 2 weeks, with an approximately 5-minute telephone call by a research coordinator to start the week following completion of their exercise intervention (approximately 5 weeks after pelvic RT) for a total of 5 calls.
- Delayed intervention cohort: Check-ins, once every 2 weeks, with an approximately 5-minute telephone call by a research coordinator starting during the first week of RT (Fx 1-5) and continue for 10 weeks for a total of 5 calls.
- The research coordinator will inquire about their use of the Fitbit device, such as if they are wearing it regularly, any technical issues, and if they are syncing their data without discussing physical activity.

9.4 Unscheduled Visits

We do not expect any unscheduled visits, but if the physician of record needs additional assessments, then these would be unrelated to the study intervention unless there is an indication that they would no longer be fit for participation in the research study due to an unanticipated change in status or patient circumstances.

9.5 Non-compliance and Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

9.5.1 The adherence to the Fitbit will be routinely monitored during exercise check-ins or during the active-monitoring check-ins and data will be recorded for analysis using the PittBit dashboard. Email reminders may be sent to participants who are found not to be wearing their Fitbit as instructed (see Appendix 6).

9.5.2 For missed visits, the site will attempt to contact the participant and reschedule the missed visit and discuss with the participant the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

9.5.3 Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

9.5.4 Should the participant continue to be unreachable, he/she/they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9.5.5 Definition of Non-compliance: A patient will be considered non-compliant to the exercise coaching intervention arm if they fail to engage in 70% of the weekly check-ins. A patient will be considered non-compliant to the

physical activity monitor if they do not wear the Fitbit activity tracker for at least 8 hours a day for 70% of the days in the study. As this is a pilot study, patients will not be removed from study due to non-compliance, as the primary outcome is to evaluate adherence.

10. STUDY ADMINISTRATION

10.1 Study Intervention(s) Administration

10.1.1 Study Intervention Description

The intervention is an exercise coaching program which will consist of weekly check-ins for 10 weeks with a certified exercise coach with expertise in caring for oncology patients. The purpose of each check-in is to address readiness for exercise, identify barriers, and develop an individualized plan for exercise for the week with a goal of increasing activity to 150 minutes of moderate activity per week using any form of activity that is enjoyable and accessible to the patient. This will be accomplished by shaping behavior through personalized recommendations. Patients will be randomized to either an immediate- or delayed-start of their exercise coaching program. Women randomized to the immediate-start group will start the intervention during the first week of radiation therapy and continue through and post-completion of radiation. Women randomized to the delayed-start group will start the intervention at 6-8 weeks post-radiation, a more typical period in survivorship where exercise counseling may begin. Participants will be asked to wear an activity monitor to track steps and moderate activity minutes and to complete assessments of patient-reported cancer-related fatigue, bowel/urinary toxicity, sexual health, and quality of life and participate in a six-minute walk test (6MWT) at predefined time points throughout the study.

Once a participant consents to the research study, they will be scheduled with the exercise coach based on their treatment group assignment (immediate or delayed start). The exercise coach will record the participation in the Epic chart, which will automatically send a message via Epic (MyChart) to the participant with instructions for their first session (Appendix 9). The participant will be asked to complete an intake form to provide the exercise coach with necessary information for their first meeting (Appendix 10). After each of the 10 coaching sessions, the exercise coach will document the encounter in Epic using the Subjective, Objective, Assessment, Postural Assessment and Observations template (SOAP; Appendix 11).

10.1.2 Study Intervention Materials

All enrolled patients will be provided with resistance bands that can be utilized for a number of exercise classes that they might be referred to by their exercise coach. All participants will receive a de-identified Fitbit device for active minute tracking. Patients will be able to keep their

resistance bands and Fitbit device after completion of the study. The device will be unregistered from the de-identified account used for study participation, and patients will be able to create their own accounts to continue to use their devices at their discretion.

10.1.3 Dosing and Administration

Not applicable.

10.2 Measures to Minimize Bias: Randomization / Blinding

Randomization will be utilized to allocate patients between early and delayed intervention arms. This study will be nonblinded to the patient given the nature of the intervention and nonblinded to the physician due to the nature of the clinical relationship, likely leading to a high chance of patient divulging of the participation in the intervention arm if they are randomized to the exercise coaching intervention. Bias with regard to patient factors will be minimized due to the use of randomization. Bias regarding the rate of activity due to Fitbit monitoring will be present in this study but assumed to be equal between the two groups as both usual care and the intervention groups will be given a Fitbit for monitoring and the use of an attention control check-ins in both intervention groups.

11. DATA COLLECTION AND MANAGEMENT

11.1 Data Collection and Management

11.1.1 Fitbit Data Collection

Each participant will be given a Fitbit device at the time of study enrollment. A de-identified Fitbit account will be created for all users, which will then be the account from which the data will be retrieved, maintaining individual patient privacy without PHI. The account username and passwords associated with their device will be de-identified. A log of the de-identified account usernames with the participant ID number will be kept in a password-protected file and stored on the research hard drive.

With appropriate consent in place, the research-allocated Fitbit device will be registered on the Fitbit Application Programming Interface (API) on the Fitbit developer site to enable scripted, automated data collection of pre-defined data elements to be collected on the study. The de-identified data of all patients will be stored and evaluated in real-time by the research team using a platform called PittBit. PittBit is a web-based application that creates a dashboard of the synched Fitbit data from participants, including active minutes, steps, and heart rate data. Each Fitbit de-identified account will be canceled and, therefore, unregistered from the API at the end of an individual participant's follow-up period so that no additional data from the Fitbit can be accessed after the study window. The participant will be able to keep their Fitbit after completing the study.

11.1.2 Storage and Future Use

Fitbit data collected on the PittBit application are de-identified. They will be limited to patient active minutes, steps, and heart rate from enrollment to the end of the follow-up time period, after which the Fitbit account created for study purposes will be canceled and unenrolled from the API. Hence, no further data collection is possible. Clinical data will be recorded in a limited dataset that will be maintained for the life of the study. The patient name will be omitted, but MRN will be retained until the dataset is completed and removed from the final dataset. Data will be maintained in a password-protected spreadsheet on the research drive, with only study team members granted access.

11.1.3 Retention/Access

Only designated research team members and the Principal Investigator will have access to PitBitt, the dataset, and the password. The data on PittBit is fully de-identified, and the study dataset will not be transferred or shared with any external institutions without amendment to this protocol and required approvals (institutional and by law). The quality management Program within the ISCI will maintain oversite of this study. The data fields retained will be listed in 11.1.4.

11.1.4 Data Fields

Data will be retrieved from:

- Fitbit Device
- EPIC
- Aria
- Raystation
- Patient web-based surveys using REDCap (or paper surveys or interview if patient preference)

Data to be collected include:

- From medical chart:
    - Variables in data tracker sheet (Appendix 12)
- FitBit Active minutes, steps, heart rate and last sync, using PittBit data platform
- Patient self-report: REDCap web-based surveys (or paper surveys or interview if patient preference) per protocol
- Subjective notes from exit interview

11.2 Security

The study is registered and approved by the Fitbit company and will be performed in compliance with both Fitbit regulations and the Inova IRB.

All personnel involved with this project are trained on the use and protection of patient information as required by Inova.

All personnel involved with study activities and/or data will have completed appropriate training in patient privacy and human subjects regulations.

A backup of the dataset will be stored as a password-protected file on Dr. Avani Rao's office computer, which remains locked when she is not directly accessing it. A backup will be retained every three months.

11.2.1 Anonymization, De-Identification and/or Destruction

Fitbit logins and passwords will be anonymous for each participant. A code will be generated for all data collected once the dataset has been validated to replace participant identifiers and maintained only by the PI and delegated research team. Fitbit data collected on the PittBit application are de-identified and will be limited to patient active minutes, steps, and heart rate from enrollment to the end of follow-up time period. Each individual Fitbit de-identified account will be cancelled and therefore unregistered from the API at the end of an individual participant's follow-up period so that no additional data from the Fitbit can be accessed after the study window. The participant will be able to keep their Fitbit after completing the study.

All data will be saved under password protection with password access granted only to the PI and critical research team members.

11.3 Release of Locally Banked Data

Not applicable.

11.4 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Inova Health System institutional policies and HIPAA on participant privacy. The Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

No identifiable data will be used for future use without first obtaining IRB approval or determination of exemption. The investigator will obtain a data use agreement between the provider of the data and any recipient researchers through the Office of Research, Business Office, before sharing a limited dataset.

All data will be kept confidential. Fitbit data collected on the PittBit application are de-identified and will be limited to patient active minutes, steps, and heart rate from enrollment to the end of follow-up time period. The study data will be stored on the research drive using password protection, which will only be accessed by the research team. When dataset is verified, the PHI will be removed and replaced with a code/participant ID that will remain in a separate password protected file.

11.4.1 Certificate of Confidentiality

Not applicable.

12. DATA ANALYTICS

12.1 Study Objectives

Primary:

The primary objective of this study is to evaluate the feasibility of conducting a randomized trial of an exercise coaching program to encourage physical activity for women treated with adjuvant pelvic intensity-modulated radiation therapy treatment for endometrial cancer.

Secondary:

1) To collect initial efficacy evaluation of the exercise coaching program on patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as well as distance walked during 6MWT between the immediate and delayed-start group from baseline to pre-specified time points (end of RT, 5-7 weeks post RT, and 16-19 weeks post RT) to guide statistical planning for follow-up study.
2) To measure the prevalence of fatigue at baseline in the population of endometrial cancer patients recommended pelvic radiation therapy using data collected in the screening process.
3) To explore potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators).

12.2 Analytics

This study will enroll 16 patients. At the Inova Schar Cancer Institute Fairfax location, approximately 24 patients will undergo a course of pelvic radiation per year. Additionally, approximately 24 patients will undergo a course of pelvic radiation per year across Inova Loudoun, Inova Alexandria, and Inova Fair Oaks Hospitals. With the goal of the study to evaluate adherence to and the acceptability and feasibility of the intervention as part of a pilot study, the sample size was determined with the goal of completing accrual of the study within one year, accruing across all four sites.

Primary Objective Analytical Plan

Feasibility of conducting a randomized trial of this nature will be evaluated on the basis of process feasibility and resources and data-management feasibility.

The *process* feasibility will be evaluated on:

1) Recruitment acceptability from the provider and patient perspective:
   a. Provider acceptability of the intervention will be defined as the proportion of patients identified on pre-screening by the PI that the primary clinician agrees of patient suitability for offering enrollment on the trial and proceeding to completion of screening steps if patient is interested in the study. We set an a priori goal of 50% provider acceptability.
   b. Patient acceptability of the intervention will be defined as the proportion

of patients who agreed to consent and then proceed to completion of screening steps. We set an a priori goal of 50% patient acceptability.

2) Appropriateness of the screening criteria:
   a. Screening criteria appropriateness will be defined as the proportion of patients who are screened who proceeded to allocation of intervention groups. We set an a priori goal of 50% of appropriateness of the screening criteria.
3) Adherence to the exercise coaching session intervention:
   a. Individual adherence to coaching sessions will be defined as complete adherence when engaging in 10 of the 10 planned exercise coaching sessions and high adherence as engaging in at least 7 of the planned 10 exercise coach check-ins. We set an a priori goal of overall 70% participant adherence to the coaching sessions, to be analyzed per cohort (6 of 8 participants in each arm demonstrating high adherence as defined above).
4) Adherence to the physical activity monitor usage to track steps and active minutes:
   a. Individual adherence to the physical activity monitor will be defined as wearing the activity tracker for at least 8 hours a day for 70% of the days in the study. Heart rate will be used to determine wear-time. We set an a priori goal of overall 70% participant adherence to the physical activity monitor, to be analyzed per cohort (6 of 8 participants in each arm demonstrating adherence as defined above).
5) Adherence to recommendation of 150 minutes per week of moderate physical activity:
   a. Individual adherence to regular physical activity will be defined as meeting the recommendation of 150 minutes of moderate physical activity per week, based on the Physical Activity Guidelines for Americans developed by the U.S. Department of Health and Human Services (HHS). The target for participant adherence is set at an a priori goal of 70%.

The *resource and management* feasibility will be assessed based on the capacity of the exercise coach and research team to perform the required tasks of the protocol:

1) Adherence to the timeline of study procedures and human and data management issues that could potentially arise during a full-scale RCT will be tracked. Adherence to the study timeline for completion of required patient surveys and 6MWT as well as appropriate scheduling (patient attendance not required) of the exercise coaching sessions and follow-ups will be a proxy measurement of research resource and human data management acceptability. We set an a priori goal of 80% adherence.

<u>Secondary Objective Analytical Plan</u>

1) Changes in patient-reported fatigue, bowel/urinary toxicity, QoL, cognitive function, sexual function and satisfaction, and self-efficacy, as well as distance walked during 6MWT from baseline to pre-specified time points (end of RT, 5-7 weeks post RT, and 16-19 weeks post RT) within and between each group will be compared using two-sample t-test or Wilcoxon Rank Sum test when appropriate. Repeated measure models/linear mixed effect models may also be used to explore the changes in self-reported questionnaires over time among different treatment groups. Data will be analyzed based on the intention-to-treat principle and used to estimate treatment effect size for future trial design.

2) Prevalence of fatigue at baseline in the population of endometrial cancer patients receiving pelvic radiation therapy will be reported using data collected in the screening process.

3) Exploratory analysis of potential behavioral mechanisms (mediators) and variables that influence the strength of the intervention effect (moderators) will be performed.

13. SAFETY MANAGEMENT

13.1 Regulatory and Ethical Considerations

13.1.1 Data and Safety Monitoring Plan

The Inova PI will monitor and review the study progress, participant safety, and the accuracy and security of the data.

13.1.1.1 Communication Plan

The DSM plan is adequate as the study will be limited to only Inova sites.

13.1.2 Risk Assessment

There is very low risk to this research intervention. The integration of exercise therapy is recommended by NCCN and ASCO for cancer patients and survivors to reduce the relapse risk and mitigate the side effects of therapy, including fatigue (2, 13). It is possible that exercise could worsen fatigue or side effects of treatment, although this likelihood is felt to be low. Patients may feel sore from activity if they were not previously active, but this would be temporary and not cause a risk of harm to the patient. As such, this study would not be greater than minimal risk of harm.

13.1.3 Potential Benefits of Trial Participation

The integrated check-ins for each arm of the trial exercise program may provide benefit in improving patient-reported outcomes and support cancer patients in a structured format. The indirect benefits of this study may be that it sets up our group to continue an exercise oncology research

program that can provide additional literature to healthcare payors for the reimbursement of exercise therapy programs for patients undergoing radiation treatments.

13.1.4 Risk-Benefit Assessment

Given that this study would be not greater than minimal risk of harm and the possibility of benefit to the patient herself and future women undergoing pelvic radiation, it is appropriate to proceed with this study.

13.2 Clinical Adverse Events

Clinical adverse events (AEs) will be monitored throughout the study.

13.2.1 Adverse Events Reporting

AEs (including serious AEs) that are felt to be study-related or possibly study-related will be noted in the study records and on the case report form with a full description including the nature, date, and time of onset, determination of non-serious versus serious, intensity, (mild, moderate, severe), duration, causality, and outcome of the event.

SAEs are not expected because the study procedures are not greater than minimal risk. If any unanticipated problems related to the research involving risks to participants or others happen during this study (including SAEs), they will be reported to the IRB in accordance with Policy – Reporting of Adverse Events, Unanticipated Problems and Protocol Violations, ORI 11.16. AEs that do not meet prompt reporting requirements will be summarized in the narrative or other format and tracked and documented internally by the study team but not submitted to the IRB.

14. PARTICIPANT COMPENSATION AND REPORTS

14.1 Participant Compensation

Patients will be awarded reloadable gift cards at enrollment and $25.00 at each follow-up time point when assessments are collected and upon completion of exit interview.

14.2 Reporting Events to Participants

14.2.1 Adverse Events

If an SAE related to the study occurs, then participating patients will be notified, and the consent form will be updated.

14.3 Study Results and Incidental Findings

It is anticipated that the results of this study will first be reported in abstract form, followed by presentation in a peer-reviewed manuscript.

15. ECONOMIC BURDENS AND COMPENSATION / INCENTIVE

15.1 Foreseeable Costs

15.1.1 Economic Burden to Participants: We do not anticipate that the study would have any costs to the participant that are required by the study.

15.2 Payments / Reimbursements

15.2.1 Reimbursement for Travel, Parking and Meals

Not applicable.

15.2.2 Payments to Participants for Time, Effort, and Inconvenience (i.e., compensation

All participants will receive a $25 gift card per survey time point and upon completion of exit interview.

15.2.3 Gifts

Fitbit devices and resistance bands will be provided to all participants free of charge, and they will be able to keep each item after completion of the study.

16. CONSENT PROCESS

16.1 Informed Consent

The consent process will occur during screening. In-person or telephone consent may be used in this study and will follow the applicable regulations. Inova's electronic consenting process is still under development at the time of this protocol development. If electronic consenting becomes an option during the time period of this study, then an amendment may be requested.

16.1.1 Waiver of Consent

Not applicable.

16.2 HIPAA Research Authorization(s)

The Inova Health System uses a stand-alone HIPAA Research Authorization compliant with federal, state, and institutional Privacy rules and regulations.

16.2.1 Waiver of HIPAA Authorization

Given the need for the PI to prescreen patients coming into the department for consultation, a partial waiver of HIPPA is requested for screening purposes (see Appendix 4).

16.3 Safeguards for Vulnerable Populations

16.3.1 Cognitively Impaired Individuals

16.3.2 Pediatric Participants

16.3.2.1 Assent

Not applicable.

16.3.2.2 Waiver of Assent

Not applicable.

16.3.2.3 Reaching Age of Majority

Not applicable.

16.3.3 Adults Unable to Consent

Given the nature of this study, adults who are unable to provide consent will not be eligible for this study as they would be at risk of being unable to participate in the intervention arm as well.

16.4 Documentation of Consent

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. A copy of the signed ICF must be available in the medical record.

17. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

Participants may withdraw from the study at any time without prejudice to their care. They may also be discontinued from the study at the discretion of the Investigator if there are any concerns for safety reasons related to the ability to participate in the study or follow-up. It will be documented whether each participant completes the study. If the Investigator becomes aware of any serious, related adverse events after the participant completes or withdraws from the study, the participants will be communicated based on the IRB's directions.

17.1 Discontinuation of Study Intervention

Discontinuation from study intervention does not mean discontinuation from the study, and the remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding related to study participation will be reported as an adverse event (AE).

17.2 Participant Discontinuation/Withdrawal from the Study

Participants may voluntarily withdraw from the study or discontinue the study

intervention at any time.

17.3 Early Termination Study Visit

When a participant is withdrawn prior to completing the study, the reason for withdrawal will be documented in a secure electronic database.

18. RECORDINGS

Not applicable.

19. IRB REVIEW HISTORY

Not applicable.

20. COORDINATING CENTER FOR MULTI-SITE STUDIES

Not applicable.

All patients will be under the care of the Inova Schar Cancer Institute, which includes campuses at Fairfax, Alexandria, Loudoun, and Fair Oaks.

21. REFERENCES / BIBLIOGRAPHY

1. Integrating Physical Activity Into Cancer Care: An Evidence-Based Approach. Bernardo L, Becker B, editors: Oncology Nursing Society; 2017.

2. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw. 2015;13(8):1012-39.

3. Evans HEL, Galvão DA, Forbes CC, Girard D, Vandelanotte C, Newton RU, et al. Acceptability and Preliminary Efficacy of a Web- and Telephone-Based Personalised Exercise Intervention for Individuals with Metastatic Prostate Cancer: The ExerciseGuide Pilot Randomised Controlled Trial. Cancers (Basel). 2021;13(23).

4. Goldstein SP, Forman EM, Butryn ML, Herbert JD. Differential Programming Needs of College Students Preferring Web-Based Versus In-Person Physical Activity Programs. Health Commun. 2018;33(12):1509-15.

5. Beleigoli A, Andrade AQ, Diniz MF, Ribeiro AL. Personalized Web-Based Weight Loss Behavior Change Program With and Without Dietitian Online Coaching for Adults With Overweight and Obesity: Randomized Controlled Trial. J Med Internet Res. 2020;22(11):e17494.

6. Alley S, Jennings C, Plotnikoff RC, Vandelanotte C. My Activity Coach - using video-coaching to assist a web-based computer-tailored physical activity intervention: a randomised controlled trial protocol. BMC Public Health. 2014;14:738.

7. Fichtner UA, Armbruster C, Bischoff M, Maiwald P, Sehlbrede M, Tinsel I, et al. Evaluation of an Interactive Web-Based Health Program for Weight Loss-A Randomized Controlled Trial. Int J Environ Res Public Health. 2022;19(22).

8. Héroux M, Watt M, McGuire KA, Berardi JM. A personalized, multi-platform nutrition, exercise, and lifestyle coaching program: A pilot in women. Internet Interv. 2017;7:16-22.

9. Granet J, Peyrusqué E, Ruiz F, Buckinx F, Abdelkader LB, Dang-Vu TT, et al. Web-Based Physical Activity Interventions Are Feasible and Beneficial Solutions to Prevent Physical and Mental Health Declines in Community-Dwelling Older Adults During Isolation Periods. J Gerontol A Biol Sci Med Sci. 2023;78(3):535-44.

10. Ng AH, Ngo-Huang A, Vidal M, Reyes-Garcia A, Liu DD, Williams JL, et al. Exercise Barriers and Adherence to Recommendations in Patients With Cancer. JCO Oncol Pract. 2021;17(7):e972-e81.

11. Schumacher O, Luo H, Taaffe DR, Galvão DA, Tang C, Chee R, et al. Effects of Exercise During Radiation Therapy on Physical Function and Treatment-Related Side Effects in Men With Prostate Cancer: A Systematic Review and Meta-Analysis. Int J Radiat Oncol Biol Phys. 2021;111(3):716-31.

12. Schumacher O, Galvao DA, Taaffe DR, Chee R, Spry N, Newton RU. Exercise modulation of tumour perfusion and hypoxia to improve radiotherapy response in prostate cancer. Prostate Cancer Prostatic Dis. 2021;24(1):1-14.

13. Schumacher O, Galvao DA, Taaffe DR, Spry N, Joseph D, Tang C, et al. Effect of Exercise Adjunct to Radiation and Androgen Deprivation Therapy on Patient-Reported Treatment Toxicity in Men With Prostate Cancer: A Secondary Analysis of 2 Randomized Controlled Trials. Pract Radiat Oncol. 2021;11(3):215-25.

14. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Semin Radiat Oncol. 2019;29(1):16-24.

15. Denlinger CS, Sanft T, Baker KS, Broderick G, Demark-Wahnefried W, Friedman DL, et al. Survivorship, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(10):1216-47.

16. Post CCB, de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, et al. Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial. Int J Radiat Oncol Biol Phys. 2021;109(4):975-86.

17. Liberman D, Mehus B, Elliott SP. Urinary adverse effects of pelvic radiotherapy. Transl Androl Urol. 2014;3(2):186-95.

18. Andreyev J. Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients. Lancet Oncol. 2007;8(11):1007-17.

19. Hilfiker R, Meichtry A, Eicher M, Nilsson Balfe L, Knols RH, Verra ML, Taeymans J. Exercise and other non-pharmaceutical interventions for cancer-related fatigue in patients during or after cancer treatment: a systematic review incorporating an indirect-comparisons meta-analysis. Br J Sports Med. 2018;52(10):651-8.

20. Mustian KM, Alfano CM, Heckler C, Kleckner AS, Kleckner IR, Leach CR, et al. Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. JAMA Oncol. 2017;3(7):961-8.

21. Cramp F, Byron-Daniel J. Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev. 2012;11:CD006145.

22. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33.

23. Ledford LRC, Lockwood S. Scope and Epidemiology of Gynecologic Cancers: An Overview. Semin Oncol Nurs. 2019;35(2):147-50.

24. Poort H, de Rooij BH, Uno H, Weng S, Ezendam NPM, van de Poll-Franse L, et al. Patterns and predictors of cancer-related fatigue in ovarian and endometrial cancers: 1-year longitudinal study. Cancer. 2020;126(15):3526-33.

25. Kang YE, Yoon JH, Park NH, Ahn YC, Lee EJ, Son CG. Prevalence of cancer-related fatigue based on severity: a systematic review and meta-analysis. Sci Rep. 2023;13(1):12815.

26. Bower JE, Lacchetti C, Alici Y, Barton DL, Bruner D, Canin BE, et al. Management of Fatigue in Adult Survivors of Cancer: ASCO-Society for Integrative Oncology Guideline Update. J Clin Oncol. 2024;42(20):2456-87.

27. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline. J Clin Oncol. 2022;40(22):2491-507.

28. Smits A, Galaal K, Winnan S, Lopes A, Bekkers RLM. Feasibility and Effectiveness of the Exercise Program in Endometrial Cancer; Feasibility and Acceptability Survivorship Trial (EPEC-FAST). Cancers (Basel). 2022;14(22).

29. McCarroll ML, Armbruster S, Frasure HE, Gothard MD, Gil KM, Kavanagh MB, et al. Self-efficacy, quality of life, and weight loss in overweight/obese endometrial cancer survivors (SUCCEED): a randomized controlled trial. Gynecol Oncol. 2014;132(2):397-402.

30. Rossi A, Garber CE, Ortiz M, Shankar V, Goldberg GL, Nevadunsky NS. Feasibility of a physical activity intervention for obese, socioculturally diverse endometrial cancer survivors. Gynecol Oncol. 2016;142(2):304-10.

31. Reynolds SA, O'Connor L, McGee A, Kilcoyne AQ, Connolly A, Mockler D, et al. Recruitment rates and strategies in exercise trials in cancer survivorship: a systematic review. J Cancer Surviv. 2024;18(4):1233-42.

32. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. Sleep. 2001;24(5):583-90.

33. Carpenter JS, Elam JL, Ridner SH, Carney PH, Cherry GJ, Cucullu HL. Sleep, fatigue, and depressive symptoms in breast cancer survivors and matched healthy women experiencing hot flashes. Oncol Nurs Forum. 2004;31(3):591-5598.

34. Patrick DL, Ferketich SL, Frame PS, Harris JJ, Hendricks CB, Levin B, et al. National Institutes of Health State-of-the-Science Conference Statement: Symptom Management in Cancer: Pain, Depression, and Fatigue, July 15-17, 2002. J Natl Cancer Inst. 2003;95(15):1110-7.

35. Stepanski EJ, Walker MS, Schwartzberg LS, Blakely LJ, Ong JC, Houts AC. The relation of trouble sleeping, depressed mood, pain, and fatigue in patients with cancer. J Clin Sleep Med. 2009;5(2):132-6.

36. Donovan KA, Jacobsen PB. Fatigue, depression, and insomnia: evidence for a symptom cluster in cancer. Semin Oncol Nurs. 2007;23(2):127-35.

37. Ligibel JA, Bohlke K, May AM, Clinton SK, Demark-Wahnefried W, Gilchrist SC, et al. Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline. Journal of Clinical Oncology. 2022;40(22):2491-507.

38. Bower JE. Cancer-related fatigue--mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597-609.

39. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res. 2009;15(2):425-30.

40. Courtier N, Gambling T, Barrett-Lee P, Mason MD. Soluble interleukin-6 receptor mediated fatigue highlights immunological heterogeneity of patients with early breast cancer who undergo radiation therapy. Adv Radiat Oncol. 2018;3(4):552-8.

41. Bower JE, Ganz PA, Tao ML, Hu W, Belin TR, Sepah S, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin Cancer Res. 2009;15(17):5534-40.

42. Bower JE, Ganz PA, Desmond KA, Bernaards C, Rowland JH, Meyerowitz BE, Belin TR. Fatigue in long-term breast carcinoma survivors: a longitudinal investigation. Cancer. 2006;106(4):751-8.

43. Bower JE, Ganz PA, Irwin MR, Kwan L, Breen EC, Cole SW. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? J Clin Oncol. 2011;29(26):3517-22.

44. Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409-26.

45. Pinto BM, Frierson GM, Rabin C, Trunzo JJ, Marcus BH. Home-based physical activity intervention for breast cancer patients. J Clin Oncol. 2005;23(15):3577-87.

46. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc. 2013;45(11):2080-90.

47. Straand IJ, Baxter KA, Følstad A. Remote Inclusion of Vulnerable Users in mHealth Intervention Design: Retrospective Case Analysis. JMIR Mhealth Uhealth. 2024;12:e55548.