LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #5

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

AMENDMENT INCORPORATES (check all that apply):

Editorial, administrative changes
Scientific changes
Study Design changes
X Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

This amendment will change the BMI inclusion criteria to help with accrual. We are decreasing the lower BMI limit of 30 to 25kg/m^2, to include both obese and overweight women as all would potentially benefit from HIIT. The upper limit will remain 55kg/m^2.

List of Updates to Protocol:

1. Updated Sections 1.1, 1.2, and 1.3 to reflect inclusion of obese/overweight women
2. Updated Section 2.2.2.2 in Exploratory Objectives to include obese/overweight analysis
3. Updated Sections 4.1 and 5.3 to reflect new BMI range of 25-55kg/m^2
4. Updated Sections 5.1, 5.3, and 5.3.6 to reflect inclusion of obese/overweight women.

***THE ATTACHED VERSION DATED September 10, 2021 INCORPORATES THE ABOVE REVISIONS* ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL**

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #4

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

AMENDMENT INCORPORATES (check all that apply):

__ Editorial, administrative changes
__ Scientific changes
_X_ Study Design changes
__ Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

This amendment changed the study design from a two-arm randomized study to a single-arm (HIIT arm only) study. This change is a result of a slower than expected accrual due to the COVID-19 pandemic. The pandemic halted all recruitment for 6 months; upon reopening new patient appointments for early stage cancers are down approximately 30%. Our team has already gained an incredible amount of insight and some good data that can be used to inform future studies to support endometrial cancer. Per the recommendation of our recent LCCC PRC review, we met with our program officer about the slower than expected accrual, and our program officer agreed with changing this study to a single arm intervention study. All new accruals will be assigned to the HIIT arm. We plan to have a total of 20 evaluable patients in the HIIT arm at the end of this study. Here, 'evaluable' means to have complete pre-HIIT and post-HIIT data.

List of Updates to Protocol:

1. Updated Sections 1.1 and 1.3 to show that this is no longer a randomized trial.
2. Removed study objectives in Section 2.1.2
3. Removed second primary endpoint in Section 3.1.2
4. Updated schema in Section 5.1 and removed mention of control arm
5. Removed all comparisons and explanations regarding the control arm in Section 5.2
6. Added mention of Complex Atypical Hyperplasia patients and removed control group comparisons in Section 5.3
7. Removed control group comparisons in Sections 5.3.5, 5.3.6 and 5.3.7
8. Time and Events Table in Section 6.1 updated to show that VO_2 is optional during post-op
9. Study Design in Section 8.1 updated to show that this is now a one arm trial with only HIIT participants
10. Sample Size Description and Data Analysis were updated in Sections 8.2

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CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #3

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

AMENDMENT INCORPORATES (check all that apply):

__ Editorial, administrative changes
__ Scientific changes
__ Study Design changes
_X_ Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

This amendment expands eligibility criteria to reflect the patients seen in our clinic. Eligibility now includes those with a diagnosis of complex endometrial hyperplasia, which has similar biology as it is a precursor to endometrial cancer. The BMI and age requirements were also updated to reflect the patient population seen in clinic and boost accrual.

List of Updates to Protocol:

1. Eligibility criteria 4.1.1 updated to include complex endometrial hyperplasia
2. Eligibility criteria 4.1.4 was deleted due to redundancy
3. Age range expanded in 4.1.2 to include patients 30 -75 years of age instead of 40-75 years old.
4. The upper limit of BMI was changed in 4.1.3 to a maximum of 55.
5. Schema 5.1 updated to indicate VO2 peak at post-surgical testing is optional.

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PROTOCOL AMENDMENT #2

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

AMENDMENT INCORPORATES (check all that apply):

_ X_ Editorial, administrative changes
___ Scientific changes
_X_ Study Design changes
_X_ Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

This amendment allows enrollment of participants with a standard of care surgery scheduled less than 3 weeks from consent date. This amendment also adjusts the intervention from HIIT session 2x a week over 3wks, to 4 to 8 total HIIT sessions. This is done to facilitate enrollment.

List of Updates to Protocol:

1. Study Synopsis 1.1: Updated to reflect change of HIIT intervention from 3 weeks to 4-8 sessions
2. Inclusion Criteria 4.1.8: Timeline of 2 days from consent to do baseline testing removed
3. Inclusion Criteria 4.1.9: Timeline for post-surgery testing and Standard of Care (SOC) visit changed to 2-4 weeks following surgery
4. Schema 5.1: Updated to reflect change of HIIT intervention from 3 weeks to 4-8 sessions, the removal of 2 days from consent to perform baseline testing, and the timeline for post-surgery testing and SOC visit. The paragraphs following schema were also updated to reflect change of HIIT intervention from 3 weeks to 4-8 sessions
5. Duration of study 5.2: Updated to reflect the varying timing of study and the change from 3 weeks to 4-8 sessions. The time on study is dictated by SOC treatment.
6. Study details 5.3: Updated to reflect change of HIIT intervention from 3 weeks to 4-8 sessions
7. Study details 5.3.6: Fasting insulin, glucose, and lipid levels removed. Clarified HgBA1C will only be collected prior to intervention
8. Time and Events table 6.1: HgBA1C delineated in table. Updated to reflect change of HIIT intervention from 3 weeks to 4-8 sessions.

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #1

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
___ Scientific changes
___ Therapy changes
_X_ Eligibility Changes

AMENDMENT RATIONALE AND SUMMARY:

This protocol amendment reflects the change in management of this study to the Lineberger Comprehensive Cancer Center Office of Clinical and Translational Research (OCTR). Study management sections were updated to reflect common practices of OCTR. Additionally, the initial study visit has been adjusted to allow the patient to complete the visit at the time of enrollment or return to a UNC exercise and sport science laboratory to complete the enrollment visit. Details have also been added to clearly identify the procedures at each time point.

List of updates to protocol:

9. The addition of endpoints and correction of formatting changed the section numbers throughout the protocol.
10. For ease of reporting in clinicaltrials.gov, the primary objectives in section 2.1 were broken apart into two separate objectives.
11. Secondary objectives were changed to Exploratory due to the nature of the endpoints.
12. Primary endpoints were added in section 3.1
13. Inclusion criteria 4.1.5 was clarified for screening purposes (previously 2.2.5)
14. Inclusion criteria 4.1.6, 4.1.7, 4.1.8, and 4.1.9 were added to ensure subject would be able to complete study activities
15. Schema and corresponding superscripts were changed in section 5.1 to clarify the events at each time point. (previously 3.1)
16. Duration of study adjusted in section 5.2 to account for the option of baseline testing at a day other than enrollment (previously 3.2)
17. Study details in section 5.3 were updated to clarify tissue procurement timing and amount (previously 3.2). Also, gift card amount was increased from $50 to $100.
18. Section 5.3 (Study Details) and 6.1 (Time and Events Table) were updated to include the use of text messaging via the CHAI-core website during the HIIT intervention.
19. Potential risks of the study were removed from previous section 4.3.8 and moved to section 7.1 in concordance with OCTR protocol structure
20. The previous time and events table was replaced to outline all study visits in Section 6.1 (previously 4.1)
21. Sections; 7.0 EXPECTED RISKS AND UNANTICPATED PROBLEMS, 8.3 Data Management/Audit, 9.2 Required documentation, 9.4 registration procedures, were updated to reflect policies of OCTR.
22. Study will be using a REDCap database so reference to that was added to Section 8.3.

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LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 1839: PRE-OPERATIVE WINDOW STUDY OF INTERVAL EXERCISE TRAINING AS A THERAPY FOR ENDOMETRIAL CANCER

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Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: 1R21CA235029-01 - Interval exercise training as a therapy for endometrial cancer

Version Date: September 10, 2021

LCCC 1839: Pre-operative Window Study of Interval Exercise Training as a Therapy for Endometrial Cancer

Principal Investigator
Victoria Bae-Jump, MD, PhD
Division of Gynecologic Oncology
University of North Carolina at Chapel Hill
[redacted]

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Version Date: September 10, 2021

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Endometrial cancer (EC) is the fourth most common cancer among women in the US. EC is increasing in frequency, due to the rising obesity epidemic. Obesity and diabetes are common factors associated with increased risk of developing EC[1-3] and increased risk of death,[4-8] with approximately 60% of EC patients being obese. In addition, **EC patients have the highest co-morbidity index among cancers and are most likely to die of cardiovascular disease.**[9, 10] Thus, improvements in cardiometabolic health are critical for decreasing mortality in EC.

Given the interplay between obesity, insulin resistance, and EC, we have explored the anti-tumorigenic effects of the anti-diabetic drug metformin. In our mouse model of EC, obesity resulted in a doubling of tumor size and increased EC lipid biosynthesis. Metformin showed increased efficacy against ECs in obese *vs.* lean mice, reversing the detrimental metabolic effects of obesity. In our phase 0 clinical trial in obese EC patients,[11] metformin decreased EC proliferation, supporting a link between metabolism and tumor biology. This work led to a phase 2/3 EC trial evaluating metformin *vs.* placebo.

Similar to metformin, a potential strategy for improving the metabolic milieu and decreasing tumor size in EC patients is to increase physical activity. High-intensity interval training (HIIT) is an exercise strategy where short intense exercise periods are interspersed with recovery periods. HIIT requires as little as 10 min of exercise per session (2 times/week) and results in rapid improvement in cardiorespiratory fitness and mitochondrial function, often in as little as 2 weeks.[12] HIIT is safe in a variety of patients, including those with heart failure,[13] stroke,[14] cancer,[15] and chronic obstructive pulmonary disease,[16] with high tolerability and few adverse events. Our preliminary evidence[17-19] suggests that HIIT is a promising approach for maximizing cardiorespiratory and metabolic adaptations, including insulin sensitivity and glycemic control, because it allows for short exercise bouts with rest periods, yet results in comparable/greater benefits to traditional moderate intensity exercise.[20, 21] Recently, pre-operative cardiorespiratory fitness has been recognized to enhance post-operative cancer recovery outcomes.[22, 23] We have previously demonstrated that a home-based HIIT intervention, before bone marrow transplant, improved cardiorespiratory fitness and transplant outcomes.[24] HIIT programs are highly adaptable and can be successfully implemented at home, with no adverse events, and yield impactful physiological outcomes. *To date, the use of HIIT in EC patients has not been previously evaluated, including the effects of HIIT on cardiometabolic health, post-operative outcomes, or as a potential novel treatment strategy for this obesity-driven disease.*

Thus, ***we will evaluate the anti-cancer effects of HIIT*** in a pre-operative window study in obese/overweight EC patients. For this trial, patients will complete 4 to 8 sessions of home-based HIIT, prior to hysterectomy. We hypothesize that HIIT will improve the metabolic environment and reduce tumor growth, as reflected in both molecular and metabolic biomarkers, specifically obesity, insulin resistance, VO_2peak, upregulation of insulin/IGF-

1 signaling, and fatty acid/lipid biosynthesis **(Fig 1)**.

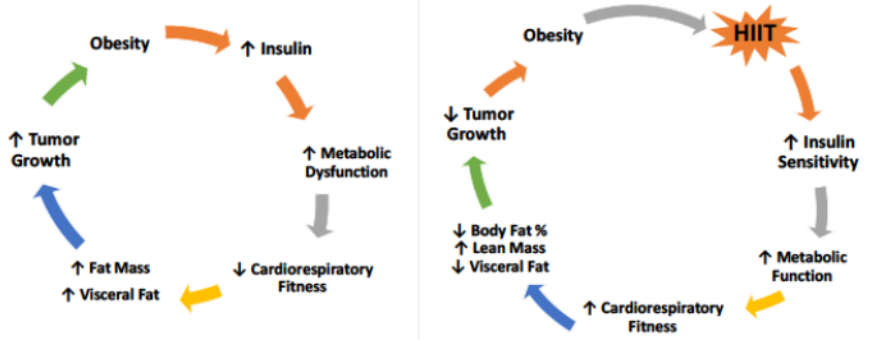


Figure 1. Theoretical model of: (A) obesity on metabolism and EC tumor growth, and (B) impact of HIIT on metabolism and EC tumor growth

1.2 Background

Endometrial cancer (EC) is the fourth most common cancer among women in the US. EC frequency is increasing, with the rising rates of obesity as the major culprit. In 2018, approximately 63,230 new cases of EC will be diagnosed in the US and 11,350 women will succumb to this disease.[25] Women with early-stage EC have a good prognosis; however, 30% of EC patients are diagnosed with advanced disease and have poor 5-year overall survival rates (15-40%). Obesity, diabetes, and insulin resistance are well-known factors associated with both increased risk of developing EC[1-3] and increased risk of death.[4-8] **Unfortunately, obese EC patients have a nine-fold higher mortality from all causes as compared to their non-obese counterparts.**[5] *Given these alarming statistics, it seems logical that interventions to combat obesity, insulin resistance, and cardiovascular disease may improve outcomes in women with EC, including metabolic targeted therapies as well as exercise and weight management.*

It is postulated that hyperglycemia and hyperinsulinemia in obese patients provide abundant nutrients and growth factors to cancer cells, resulting in an ideal environment for signaling cascades, such as the insulin/insulin-like growth factor-1 (IGF-1) and PI3K/Akt/mTOR pathways.[26] Hyperinsulinemia, IGF-1, and IGF-1 receptor (IGF1R) levels are important in EC development and progression.[27, 28] Signaling through IGF-1R leads to activation of the PI3K/Akt/mTOR pathway, and components of this pathway are often mutated, amplified, or aberrantly expressed in EC.[29-32] In addition, mitochondrial dysfunction is a hallmark of cancer cells, resulting in decreased oxidative phosphorylation and increased glycolysis.[33-35]

In addition to greater body fat, obese individuals have increased visceral fat, which is associated with insulin resistance and alterations in metabolic signaling pathways leading to increased adipokine and inflammatory cytokine production, induction of lipolysis and greater release of free fatty acids into the circulation.[36, 37] There is high demand for fatty acids by tumor cells as these are critical for building the lipid membrane bilayers in rapidly proliferating cells.[36, 37] Thus, increased production of fatty acids is another mechanism by

which obesity fuels tumor growth. *In summary, obesity creates a unique tumor-enhancing environment that should be strategically and therapeutically targeted to improve outcomes for obese/overweight EC patients. Potential interventions include metformin as explored in our previous work and HIIT as will be explored in this proposal.*

Metformin has anti-EC effects. Given the interplay between obesity, insulin resistance, and EC, we have explored the anti-tumorigenic effects of the anti-diabetic drug metformin in pre-clinical EC models. Metformin is thought to have anti-tumorigenic effects *via* decreasing circulating insulin/glucose levels, inhibiting mitochondrial complex I, activating AMPK and inhibiting insulin/IGF-1/mTOR and lipid signaling pathways. In our $LKB1^{fl/fl}p53^{fl/fl}$ mouse model of EC, obesity resulted in a doubling of tumor size and increased EC lipid biosynthesis (manuscript in prep).[38] Mirroring our $LKB1^{fl/fl}p53^{fl/fl}$ metabolomic findings in mice, alterations in the expression of metabolically relevant genes related to lipid metabolism and to the insulin/IGF-1 signaling pathway in endometrioid ECs were associated with elevated BMI in The Cancer Genome Atlas (TCGA) database.[39] Metformin had increased efficacy against ECs in obese vs. lean mice, reversing the detrimental metabolic effects of obesity in the tumors via shunting fatty acids to beta-oxidation as opposed to lipid biosynthesis **(Fig 2)**.[38] We hypothesize that this metabolic obese signature underlies metformin's improved efficacy in treating obesity-driven tumors.

In our phase 0 clinical trial in obese EC patients,[11] we found a favorable response to short-term metformin treatment, including reduced proliferation and decreased expression of the IGF-1 receptor and targets of AMPK/mTOR pathway. Metformin responders had higher pre-treatment levels of fatty acids/glycolipids in their serum, suggestive of a more insulin resistance phenotype predicting increased benefit to this drug. Together, these findings support a link between metabolism and tumor biology. This work led to a phase 2/3 EC trial evaluating metformin vs. placebo plus paclitaxel/carboplatin in advanced/recurrent endometrial cancer (GOG286B). *In a similar phase 0 clinical trial, we propose to assess*

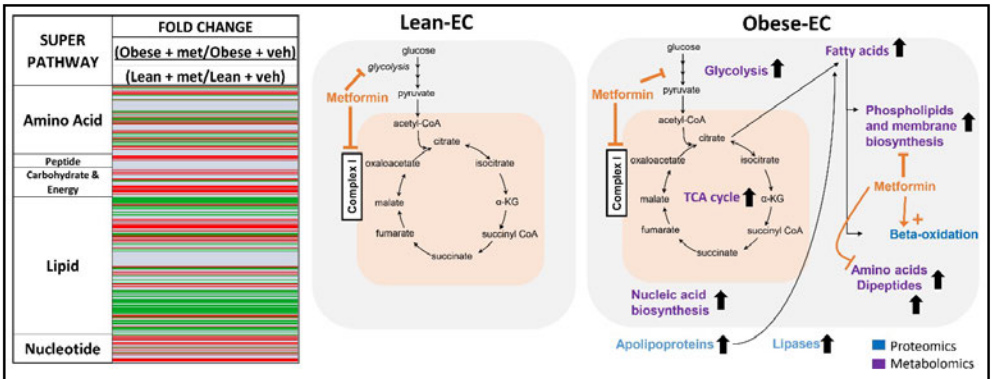


Figure 2. Schematic of the impact of obesity on the endometrial tumors in $LKB1^{fl/fl}p53^{fl/fl}$ mice and resulting effect of metformin treatment. Metformin reverses obesity-driven upregulation of lipid biosynthesis *via* shunting of free fatty acids to beta-oxidation. Red=increased; Green=decreased

HIIT as a metabolic treatment of EC.

HIIT as a therapeutic intervention for EC. Although metformin shows promise in the treatment of EC, another innovative approach would be an exercise intervention that may

similarly impact EC growth through improvements of the metabolic environment of the patients and their tumors. In parallel, exercise interventions may also affect long-term cardiovascular outcomes in EC patients as well as uniquely improve post-operative outcomes, as hysterectomy is most often the first step in treatment. We have previously shown that 70% of EC survivors are motivated to make behavioral change following their cancer diagnosis, but have a low success rate of increasing physical activity and losing weight without intervention.[40] Unfortunately, exercise and weight management strategies are rarely integrated into EC care, mostly due to the lack of resources and burdens in delivery of these interventions.

HIIT has gained attention as a time-efficient and effective method for improving body composition and augmenting cardiorespiratory health in a variety of populations, including the obese/overweight and clinical populations.[41, 42] HIIT has been shown to stimulate a number of skeletal muscle adaptations that augment fat oxidation and oxygen utilization.[41] As a result of enhanced mitochondrial biogenesis and upregulated enzymes, a number of metabolic parameters are improved following interval training.[42] Many recent studies have demonstrated that shorter duration interval based exercise (30 sec – 4 min) may be more advantageous than traditional continuous exercise, resulting in greater improvements in cardiorespiratory fitness, skeletal muscle oxidative capacity, and a concomitant improvement in insulin sensitivity.[43-46] HIIT has previously been shown to increase skeletal muscle mitochondrial biogenesis following a single session.[47] Due to the underlying mitochondrial dysfunction observed in EC tumor cells, HIIT may be an effective strategy to rapidly improve mitochondrial function prior to surgery. Importantly, HIIT programs are highly adaptable, and can be successfully implemented at home with no adverse events, and still yield impactful physiological outcomes. Home-based training utilizing higher intensity intervals of exercise may offer several advantages, including modifications to fit the needs of patients, adaptability to the home setting, and requirement of less overall time than traditional approaches to improve fitness. Our preliminary data have demonstrated that in overweight and obese adults (20-50 years old), 3 wks of HIIT results in significant improvements in markers of cardiovascular health (8.7% increase in VO_2peak), triglycerides (6.9% decrease), HDL (2.3% increase), and insulin (15.5% decrease) (**Fig 3**).[18, 19] We have also demonstrated that HIIT is feasible in pre-bone marrow transplant patients, with 70% completing 6 wks of training prior to transplant.[24] Collectively, these preliminary data show the overall feasibility of HIIT, supporting the high applicability of HIIT in an obese/overweight population with EC.

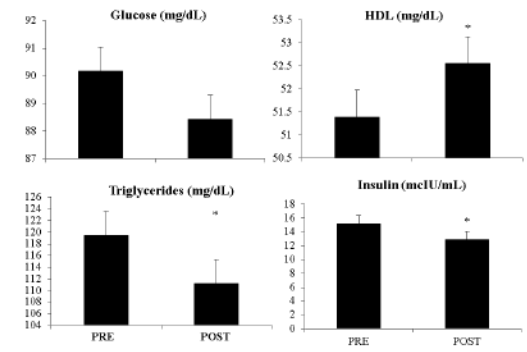


Figure 3. Metabolic blood markers before (PRE) and after (POST) 3-wks of HIIT in overweight/obese subjects.

INNOVATION: (1) We will use a pre-operative window study design to assess the efficacy of HIIT in inhibiting EC proliferation that will also include an assessment of

potential molecular and metabolic biomarkers of response to this therapy. This study is innovative in that it will delineate the effect of HIIT on endometrial tumor growth and intra-tumoral insulin/lipid signaling pathways as well as the cardiometabolic health of EC patients. *This will be the first trial of HIIT in EC patients.*

(2) HIIT is a well-tolerated, time-efficient, and effective exercise approach that rapidly improves cardiorespiratory fitness, hyperinsulinemia, hyperlipidemia, and body composition, which may be particularly useful in obesity-driven EC.

(3) Unique aspects of HIIT include that it requires minimal time commitment (10 min of exercise 2 times/wk) and is tailored to individuals based on baseline abilities (following a well-developed protocol), making it a program likely to be sustainable and tolerable for women with EC.

(4) HIIT is a major departure from the way physical activity is recommended for EC patients. Initial discoveries from this study could facilitate a change in pre- and post-operative approaches for the management of EC.

1.3 Purpose and Rationale

To date, the use of HIIT in EC patients has not been previously evaluated, including the effects of HIIT on cardiometabolic health, post-operative outcomes, or as a potential novel treatment strategy for this obesity-driven disease. Thus, we will evaluate the anti-cancer effects of HIIT in a pre-operative window study in obese EC patients. We hypothesize that HIIT will improve the metabolic environment and reduce tumor growth, as reflected in both molecular and metabolic biomarkers, specifically obesity/overweight, insulin resistance, VO_2peak, upregulation of insulin/IGF-1 signaling, and fatty acid/lipid biosynthesis.

If the HIIT intervention is efficacious in inhibiting tumor growth/proliferation and improving the metabolic environment of obese/overweight women, future studies would explore its use as (1) an adjunct to traditional radiation/chemotherapy treatment, (2) an obesity/overweight management strategy in EC survivors, and (3) a pre-operative strategy to optimize surgical outcomes. These efforts have great potential to break the obesity-EC link, ultimately improving outcomes for EC patients.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 Determine the anti-proliferative effect of HIIT on the endometrium of women with EC by comparing endometrial biopsy samples of patients

before undergoing a HIIT intervention to their post-HIIT endometrial tissue/hysterectomy specimens.

2.2 Exploratory Objectives

[redacted]

3.0 STUDY ENDPOINTS

3.1 Primary Endpoints

3.1.1 Change in Ki-67 proliferation values within HIIT intervention group between initial biopsy and surgical biopsy

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Patients with a diagnosis of endometrioid histology cancer or complex endometrial hyperplasia who are to undergo hysterectomy and staging

4.1.2 Between 30-75 years old

4.1.3 Body mass index of 25-55 kg/m^2

4.1.4 Presumed clinically early stage disease (disease confined to uterus only)

4.1.5 Have access to a Smart Phone

4.1.6 Have access to email

4.1.7 Agree to visit the exercise and sport science laboratory prior to surgery for baseline testing if enrollment procedures cannot be done on the same day.

4.1.8 Agree to visit clinic 2 to 4 weeks after surgery for SOC follow-up and post surgery visit, or willing to return to exercise and sport science laboratory 2 to 4 weeks post-surgery

4.2 Exclusion Criteria

4.2.1 Meets American College of Sports Medicine Guidelines for physical activity (150 minutes / week)

4.2.2 Currently doing HIIT

4.2.3 Hospitalization for a stroke, heart attack, or heart failure, or had surgery for blocked arteries in the past 3 months

4.2.4 Active diagnosis of psychosis or current uncontrolled substance abuse disorder

4.2.5 Insulin-dependent diabetes

4.2.6 Currently in another EC intervention

4.2.7 Severe dementia or other memory loss condition

4.2.8 Severe mental health disorder

4.2.9 Severely impaired hearing or speech

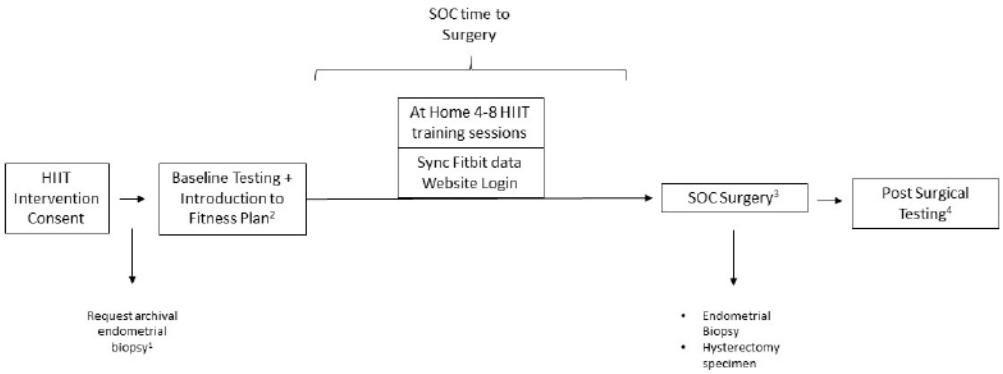
4.2.10 Inability to speak English

4.2.11 Musculoskeletal or neuromuscular condition that limits physical activity

4.2.12 Any condition, in the opinion of the investigators, which would prohibit safe participation.

5.0 STUDY PLAN

5.1 Schema



[1]After consent, study coordinator can request archival endometrial biopsy
[2]Details of testing measurements are available in the Time and Events Table. The baseline testing visit can occur either at the clinic visit or the participant can return to the exercise physiology lab in Fetzer Hall. Subjects will receive instruction on their personalized HIIT intervention. The personalized HIIT intervention will be adjusted so the participants can complete 4-8 HIIT sessions, with 24 hours of rest time, prior to surgery.
[3]Surgery will take place per SOC and will not be dictated by the study. Endometrial biopsy will take place after sedation by surgeon, hysterectomy specimen will be removed as part of SOC testing
[4]Post-surgical testing and SOC post-surgical visit will take place 2-4 weeks after SOC surgery. The VO_2 peak testing is optional at this visit.

This project is a phase 0 clinical trial in which all patients who undergo surgical staging for EC will participate in the HIIT intervention group that will complete 4 to 8 sessions of home-based HIIT prior to hysterectomy. The effect of HIIT on proliferation and apoptosis will be compared between pre-intervention endometrial biopsies and post-intervention endometrial tissue/hysterectomy specimens. Expression of regulators of insulin/IGF-1/fatty acid/lipid synthesis pathways will be compared pre- and post-HIIT intervention in ECs.

Based on our preliminary data, HIIT should rapidly lead to improvements in cardiometabolic health in EC patients within 4 to 8 sessions (approximately 2-3 wks of HIIT). To assess the benefits of HIIT in EC, we propose a comprehensive assessment of

cardiovascular and metabolic biomarkers of HIIT response among women enrolled in this phase 0 study that includes traditional (VO_2peak, BMI, HgBA1C) and novel (metabolomic profiling) assessments of obesity/overweight, insulin resistance, and cardiorespiratory fitness.

We predict that the HIIT intervention will result in decreased proliferation and increased apoptosis when comparing tumors pre- and post-HIIT. Based on our experience with this HIIT protocol in various special populations, EC patients are anticipated to demonstrate good compliance and report sufficient tolerability to the intervention. In addition, we anticipate that hyperactivation of the insulin/IGF-1/AMPK/mTOR pathway and stimulation of fatty acid/lipid biosynthetic pathways will be found in the endometrial tumors pre-HIIT, and HIIT therapy will result in inhibition of downstream targets of these metabolic pathways. Moreover, we expect BMI, waist-to-hip ratio, and HgBA1C to decrease. Elevated pre-treatment serum levels of fatty acids and glycolipids should be found in those obese/overweightwomen who best respond to HIIT, indicative of a more insulin-resistant metabolic phenotype in HIIT-responders. This insulin resistant metabolic profile should improve with HIIT treatment.

5.2 Duration of Study

This study will last approximately 10 weeks total. During a SOC visit, subjects will be consented prior to hysterectomy. HIIT exercise will be a home-based program in the intervening weeks between SOC clinic visit and SOC surgery. Subjects can undergo baseline testing on the day of their SOC appointment in the North Carolina Cancer Hospital, or return to an exercise physiology lab in Fetzer Hall after their consent visit. All subjects will be directed to complete 4 to 8 sessions of the at home exercise program, log exercise in study website, and sync Fitbit data. At SOC surgery, endometrial biopsy and hysterectomy specimens will be collected. At a SOC post-operative appointment, 2 to 4 weeks post-surgery, post-testing will occur for all subjects.

5.3 Study Details

Obese and overweight (BMI≥25-55 kg/m^2) women with type I EC (endometrioid histology) and complex atypical hyperplasia (CAH) will be recruited from the Gynecologic Oncology clinic at UNC-CH. The Division of Gynecologic Oncology at UNC-CH of which Dr. Bae-Jump is a member has 10 clinically active gynecologic oncologists who care for and treat about 250 women per year with newly diagnosed EC. Obesity rates among the EC patients treated at UNC are approximately 62%, with most of remaining women being overweight. Thus, recruitment to this clinical trial should be successful in 12-18 months. Our previous reported phase 0 clinical trial of metformin easily recruited 20 patients in 12 months.

Women with endometrial cancer or complex atypical hyperplasia are usually diagnosed by endometrial biopsy either obtained in the office using a pipelle device or in the operating room by dilation and curettage (D&C). Our standard practice for outside endometrial biopsies is to obtain the blocks and have the biopsies reviewed by the pathologists at UNC-CH for confirmation of diagnosis. Therefore, all pre-operative endometrial biopsies,

whether obtained at UNC-CH or at a referring institution, will be available for analysis in this study. The preferred treatment management for women with EC and CAH is surgical staging, which includes total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Once enrolled on this pre-operative window study, patients will undergo baseline physiological testing to determine peak cardiorespiratory fitness (VO_2peak) and maximum heart rate (HR). This physiological testing will then be used to construct an individualized HIIT intervention, consisting of 4 to 8 at-home training sessions, which will be completed prior to surgical staging. The effect of HIIT will be compared between pre-treatment endometrial biopsies and their corresponding post-treatment hysterectomy specimens, with proliferation (i.e. Ki-67 staining) as the primary endpoint of interest. In addition, enrolled patients will undergo repeat endometrial biopsy post-HIIT intervention at the time of their surgical staging; this is being done to ensure that we are accurately evaluating the effects of the HIIT intervention on the endometrial tumors themselves and not differences found due to the type of specimen examined (i.e. endometrial biopsy specimen obtained in clinic versus hysterectomy specimen obtained at the time of surgery). Thus, we plan to compare pre-treatment endometrial biopsies to both post-treatment endometrial biopsies and hysterectomy specimens. Efficacy, tolerability, adherence, and exercise enjoyment will be assessed before and after the intervention as secondary outcomes. All women enrolled will receive a $100 gift card for participating in this study.

Potential prospective subjects will be identified in the following ways: study staff may review the medical records of patients listed on the clinic schedule to determine if a patient meets eligibility criteria for this research study prior to the patient meeting with the physician. Alternatively, patients may be referred to the research team by their UNC physician, outside physician, self-refer or may be discussed at disease specific conferences. In all cases, a member of the research team will review the medical record to see if the patient meets basic eligibility criteria. The patient's physician will present options to the patient and, if the patient is interested, the research study coordinator will consent the patient and HIPAA authorization will be sought.

Potential prospective subjects will be seen in private clinic rooms by the physician and the team member that will be informing and consenting the subject. The purpose of this study and the risks and side effects of HIIT therapy will be addressed in the consent and verbally explained to the patients. The purpose of serum and tissue collection and the risk to these procedures will be verbally explained to the patients. Informed consent will be obtained from the patients by the study coordinator.

In order to ensure retention of subjects during the proposed HIIT intervention, subjects will be contacted weekly by study staff. These scheduled calls or text messages will ensure that the subjects have no questions about the intervention, that they are tolerating HIIT without any significant adverse effects, that they are syncing their Fitbits, and to make sure they are logging in their exercises on the website every time they work out. Furthermore, subjects will be provided multiple contact numbers for study personnel to contact with questions or concerns about the HIIT intervention (day or night).

After women have undergone hysterectomy/surgical staging for EC or CAH, their corresponding pre-treatment endometrial biopsies and post-treatment endometrial tissue/hysterectomy specimens will be obtained for comparison. Hysterectomy/tumor and repeat endometrial biopsy specimens from the EC and CAH patients in the operating room will be collected via the Tissue Procurement Core Facility (TPF) at the Lineberger Comprehensive Cancer Center (LCCC). In addition, the pre-operative endometrial biopsy slides and blocks will be obtained from referring physicians of these patients for analysis in this study. All patients would have had an endometrial biopsy performed prior to referral to the Gynecologic Oncology clinic as part of their diagnosis of endometrial cancer or complex atypical hyperplasia. Blood (10mL) and urine will be collected pre- and post-HIIT intervention for metabolomic profiling as a strategy to identify other potential biomarkers of response to HIIT. Fresh EC tissue will be collected post-HIIT intervention via hysterectomy for metabolomic profiling and correlation with metabolic changes in serum. These biospecimens will be stored indefinitely for research purposes unless the participant refuses to agree to storage for future use on the informed consent form.

HIIT Intervention: Following the VO_2peak testing, patients will be provided with a FitBit HR2+ wristband accelerometer to track heart rate training zone and view their physical activity throughout the study. Patients will be counseled by the study exercise physiologist (PI, Smith-Ryan) to discuss available local training resources (e.g. walking, jogging, aerobic exercise equipment) depending on individual patient lifestyle and preferences (**Fig 4**). The selected exercise-training mode for each patient will be used for that patient's HIIT throughout the study. Patients will be instructed on how to achieve their individual prescribed training zone [85-95% maximal heart rate (MHR)] that will be calculated based on VO_2peak assessment and pre-programed into the wrist monitor. Participants will be asked to undergo 4 to 8 sessions of home-based interval fitness bouts. The exercise will consist of a 5-min warm-up, followed by 10 1-min intervals at 85-95% MHR within each bout, separated by 1-min low intensity (50% MHR) or complete rest. Participants will document each interval session by electronically logging data into the study website (exercisenutritionasmedicine.com) on the CHAI-core web platform. They will be emailed information to login to the website. This site will automatically upload activity data from the FitBit, as well as provide reminders to complete HIIT and display HR goals. The site will also be used to send text messages reminding participants to track and complete their exercise, charge and sync their FitBits, and to aim for their target HR. This messaging will not include any protected health information and standard messaging rates will apply. During this same visit, total body composition and visceral fat will be assessed using brightness-mode ultrasound (Logiq-e, GE Healthcare, Wisconsin, USA) as previously validated.[48]

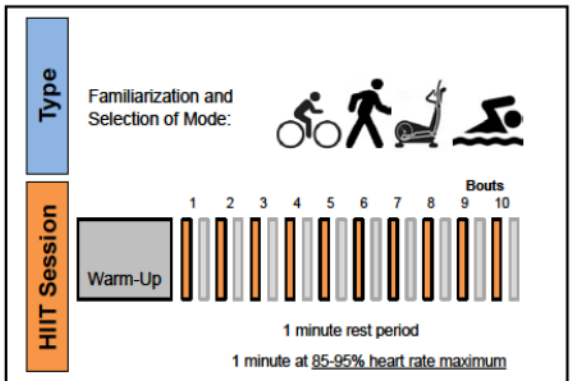


Figure 4. Schematic of HIIT intervention in a randomized phase 0 trial in obese EC patients.

5.3.1 Structured Interview:

A structured one-on-one interview will occur with participants after completion of the HIIT program. The interview will be used to learn about barriers and concerns they experienced with regard to the current training protocol; preference of exercise mode and instruction; and opinions on what information participants would find helpful to improve the at-home training experience. While we do not intend to formally analyze the interview responses, we do anticipate that they will be useful for refining our intervention program for future trials.

5.3.2 Tolerability, Feasibility, Compliance, and Adherence: Adherence and tolerability will be evaluated based on number of sessions attended/completed, modifications, such as change in mode, number of training days per week, and recovery days needed between sessions to complete training. The physical activity enjoyment scale[49] will be given to assess participant enjoyment of exercise during the baseline and post-surgical testing visit.

5.3.3 To determine if HIIT decreases proliferation and induces apoptosis in the endometrial tumors, tissue microarrays (TMAs) will be constructed and immunohistochemical (IHC)analysis performed to assess Ki-67 staining (marker of proliferation) and caspase-3 expression (marker of apoptosis). The percentage of Ki-67 positive cells, termed the Ki-67 index, will be calculated pre- and post-treatment. Apoptosis will be evaluated by changes in activated caspase-3 expression. Individual slides will be digitized and analyzed using the Aperio ScanScope (Aperio Technologies, Vista, CA). This work will be performed with the expertise of the UNC-CH Translational Pathology Lab (TPL).

5.3.4 To test if HIIT alterations inhibits downstream targets of the insulin/IGF-1/AMPK/mTOR signaling pathway, IHC analyses of the ECs will be performed to determine expression of key targets of the insulin/IGF-1/mTOR pathway pre- and post-intervention, including p-IRS-1, p-IGF1R, p-AMPK, p-mTOR, p-Akt, p-S6, and p-4EBP-1.

5.3.5 To assess improvement in cardiorespiratory fitness with the HIIT intervention, peak oxygen consumption (VO_2peak) will be measured pre- and post-HIIT. VO_2peak is the gold standard for identifying fitness level and evaluating cardiovascular effects. This test will be used to establish individual training intensity. All participants will perform a ramp based cycling ergometer test with respiratory gases continuously monitored with open-circuit spirometry using a calibrated metabolic cart (True One 2400®, Parvo-Medics, Inc., Provo, UT). Data will be averaged over 15-second intervals, with the highest 15-sec oxygen consumption, minute ventilation, and heart

rate recorded as the peak oxygen consumption (VO_2peak), time to exhaustion, and maximum heart rate, respectively**.**

5.3.6 To correlate improvement in obesity/overweight and insulin resistance with response to HIIT treatment, BMI, waist-to-hip ratio, body composition, HgBA1C, and diabetes status will be documented pre- and post-intervention. HgBA1C will be obtained pre-intervention only for all subjects. Body composition and visceral fat will be determined using portable ultrasonography as previously validated by our group.[48] The Homeostasis Model Assessment Score [fasting insulin (microunits/ml) X fasting glucose (mmol/22.5)], a measurement of insulin resistance, will be calculated prior to and after the intervention.

5.3.7 To test if the metabolic profiles of blood and tumor correspond to HIIT responsiveness, untargeted metabolomic/lipidomic analysis will be performed on (1) blood pre- and post- HIIT and (2) tumor pre- and post-HIIT intervention. Metabolic profiles of blood and tumor will be compared between pre- and post-intervention and the HIIT group. Untargeted metabolomic and lipidomic profiling will be performed using Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy (UPLC-MS-MS) and Differential Mobility Spectroscopy-MS-MS (DMS-MS-MS). Urine is also being banked pre- and post-HIIT intervention for potential future metabolomic/lipidomic analysis.

5.3.8 Removal of Patients from Protocol - Patients will be removed from the study if they indicate that they no longer wish to participate. Patients will be removed from study when any of the exclusion criteria listed in eligibility criteria apply.

6.0 TIME AND EVENTS TABLE

6.1 Time and Events Table

	Pre-op or New visit	Baseline Testing Visit[1]	At home intervention[2]	Surgery	Post Surgical Testing Visit
	SOC appointment	During SOC appointment or at Applied Physiology Lab	4 to 8 Sessions	As scheduled per SOC	SOC appointment 2 to 4 wks post-surgery
Consent	X				
Eligibility Assessment	X				
Archival Tissue Retrieval	X				
Urine Sample	X			X	
Blood Sample	X			X	
Enrollment		X			
Waist and Hip Measurements		X			X
VO2peak		X			X[3]
Body Mass ultrasound		X			X
Visceral fat ultrasound		X			X
Fitbit Fitting		X			
Introduction to Fitness Plan		X			
Exercise Enjoyment Scale		X			X
Completion of Fitness plan			X		
Sync Fitbit data			X		
Participant Website Login			X		
Endometrial biopsy				X	
Hysterectomy Specimen				X	
Closing interview					X

[1]Baseline visit can occur during SOC visit at time of consent and enrollment, or the subject will have the option to return to campus and perform visit at the exercise physiology lab at Fetzer Hall. If subject commits to return for baseline visit, but fails to return, the subject will not be enrolled on the study, and a new subject can be enrolled in that spot.
[2]At home intervention begins with first HIIT session. During this time, subject will be called or texted by the study team to remind the subject to login to website, sync data, and troubleshoot technical difficulties.
[3]The VO_2 peak testing is optional at this visit.

7.0 EXPECTED RISKS AND UNANTICIPATED PROBLEMS

7.1 Expected Risks:

7.1.1 HIIT:

The risks of short-term HIIT treatment are minimal for these patients. Mild muscle soreness associated with beginning any new exercise program is possible. The exercise program will be individualized for each patient, reducing the chances of soreness. With any exercise, there is a small risk for syncope, as well a cardiovascular event. Because of the short nature of the high intensity bouts, risk of syncope is reduced; rest periods also allow for greater blood flow, reducing risk of syncope. Patients at risk for any such cardiovascular event will be excluded. These types of adverse events as a result of HIIT, are extremely rare.

7.1.2 Blood Draws & Urine Collection:

Patients will need to undergo blood draws at the beginning and end of HIIT treatment. The second blood draw will be done under general anesthesia at the time of surgical staging. Risks to blood draws are minimal and include pain and discomfort, infection and hematoma. Thus, these women have little increased risk secondary to blood draws. Blood will be obtained by phlebotomists or by anesthesiologists/nurse anesthetists in the operating room. Patients will need to undergo urine collection at the beginning and end of HIIT treatment. Risks to urine collection are minimal.

7.1.3 Endometrial biopsy:

Endometrial Biopsy is a common gynecologic procedure performed in the outpatient setting. The risks of repeat endometrial biopsy at the time of surgery are minimal for these patients, given that they will be under general anesthesia and are to undergo immediate hysterectomy. Endometrial biopsy will be performed using a standard pipelle device, routinely used in our outpatient clinic. The most common risks to the patient for this procedure are cramping and a vaso-vagal response. Other much rarer risks include uterine bleeding (usually due to previously undiagnosed coagulopathies), uterine perforation (0.1 – 1.3%), pelvic infection and bacteremia (<1%). These patients will already be familiar with the procedure of endometrial

7.1.4 Breach of Confidentiality:

Research data will be stored in a secure, password-protected server accessible solely to trained study staff. All data and specimens stored in the research database will be given a unique research ID that will be blinded to investigators with the exception of the Study Coordinator, who will function as an honest broker. The Study Coordinator will be trained and certified in research ethics and HIPAA tenets.

7.2 Definition

As defined by UNC's IRB, unanticipated problems involving risks to study subjects or others (UPIRSO) refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

7.3 Reporting

Any UPIRSO that occurs during the conduct of this study and that meets all three criteria listed in 9.4.3 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC) as required.

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc. and the team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This project was originally designed as a randomized, prospective, phase 0 clinical trial in which half of the patients who undergo surgical staging for EC will be

randomized to a HIIT intervention group receiving 4 to 8 session of home-based HIIT (approximately 2-3 wks of HIIT), and the other half receiving standard of care treatment (i.e. no exercise intervention), prior to hysterectomy. The effect of HIIT on proliferation and apoptosis will be compared between pre-intervention endometrial biopsies and post-intervention hysterectomy/endometrial biopsy specimens. Expression of regulators of insulin/IGF-1/fatty acid/lipid synthesis pathways will be compared pre- and post-HIIT intervention in ECs.

Slow accrual due to COVID-19 pandemic prevent us from completing the study in time. As COVID-19 pandemic is still on-going, we decided to change the study design to a prospective single arm study with all new accruals assigned to the HIIT arm, till we have a total of 20 evaluable (i.e., with complete pre- and post-HIIT data) patients in the HIIT arm.

8.2 Sample Size and Accrual

The original sample size description: Based on data from our previous studies,[11, 50] we expect a difference of 13% (SD = 14%) for pre-post change in Ki-67 proliferation, and a difference of 1.7 (SD = 1.8) $ml \cdot kg \cdot min^{-1}$ for pre-post change in VO_2peak, and attrition not greater than 10%. Under these assumptions, having 22 (20 evaluable) subjects per arm would detect the expected differences in both primary endpoints with at least 75% power and 2-sided α=0.025 (Bonferroni adjustment).

The updated sample size description: Based on data from our previous studies,[11, 50] we expect a difference of 10.3% (SD = 14%) for pre-post change in Ki-67 proliferation, and a difference of 1.8 (SD = 2.5) $ml \cdot kg \cdot min^{-1}$ for pre-post change in VO_2peak in the HIIT arm, and attrition not greater than 10%. Historically, the pre-post change in Ki-67 and in VO_2peak under usual care are 0. Under these assumptions, having 20 evaluable subjects in the HIIT arm would detect the expected differences in both primary endpoints with at least 80% power and 2-sided α=0.025 (Bonferroni adjustment).

Data Analysis Plans

The original data analysis plan: Appropriate descriptive statistics for relevant variables (e.g., Ki-67 proliferation, VO_2peak, p-mTOR expression, time to exhaustion, etc.) will be calculated by arm and by time (baseline and week 3). For pre-post changes of Ki-67 and VO_2peak, the two primary endpoints (and similarly for other variables), differences between groups (HIIT vs. no-HIIT) in Ki-67 (or VO_2peak) will be analyzed using analysis of covariance (ANCOVA) with baseline Ki-67 (or VO_2peak) used as the covariate.

Our primary analysis will follow the intent-to-treat (ITT) principle, like for many randomized clinical trials. For the primary analysis, we will use a conservative (but valid) approach, and only include key covariates like baseline Ki67 level, stratification factors, in addition to HIIT (treatment assignment). In the exploratory

analysis, we will include adherence and other covariates in the model. Findings from exploratory analysis will be used for hypothesis generation.

The updated data analysis plan: Appropriate descriptive statistics for relevant variables (e.g., Ki-67 proliferation, VO_2peak, p-mTOR expression, time to exhaustion, etc.) will be calculated by arm and by time (baseline and week 3).

Our primary analysis will be on pre-post changes in Ki-67 and VO_2peak for patients in the HIIT arm and to test whether the differences were significantly different from 0 using Wilcoxon signed rank test.

For now, there are 10 patients randomized to the usual care arm have completed the study. To make good use of the data, we will conduct an exploratory analysis to compare the differences between groups (HIIT vs. no-HIIT) in Ki-67 (or VO_2peak), which will be analyzed using analysis of covariance (ANCOVA) with baseline Ki-67 (or VO_2peak) used as the covariate (we will also conduct similar exploratory analyses for other variables). We may also include adherence and other covariates in the model. Findings from exploratory analysis will be used for hypothesis generation.

8.3 Data Management/Audit

The Office of Clinical & Translational Research (OCTR) will serve as the coordinating center for this trial. Data will be stored in a secure, password-protected, web-based platform using REDCap maintained by the North Carolina Translational and Clinical Sciences Institute (NCTraCS) and accessible solely to trained study staff. Synced Fitbit data, as well as website data entry by participants, will also be securely stored and password-protected by CHAI Core, an NHI-funded core facility that provides services in behavioral intervention research. Participant data files collected via the study coordinator will be kept in one analytic data set that will combine all clinical and demographic data and related tissue data as a de-identified dataset for analysis. The link between the participant's identifying and research information will be kept separate from data files and secure. This analytic data set will be placed on a secure server for retrieval by the study investigator/analyst.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment into this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Office of Clinical & Translational Research (OCTR) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol
- A copy of the IRB-approved consent form

9.3 Registration Procedures

All subjects must be registered with the Lineberger Comprehensive Cancer Center, and entered into the web based clinical research platform, Oncore®.

9.4 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.4.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC IRB approval.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

9.4.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any

circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

9.4.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore® (or other appropriate database set up for the study), and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report UPIRSO.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSO:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB (see section 7.2) must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.5 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

9.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.7 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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