The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Randomized trial comparing telephone vs. in-person weight loss counseling on body composition and circulating biomarkers in women treated for breast cancer: The Lifestyle, Exercise and Nutrition (LEAN) Study

Harrigan, et al

DOI: 10.1200/JCO.2015.61.6375

The information provided may not reflect the complete protocol or any previous amendments or modifications. As described in the Information for Contributors (http://jco.ascopubs.org/site/ifc/protocol.xhtml) only specific elements of the most recent version of the protocol are requested by *JCO*. The protocol information is not intended to replace good clinical judgment in selecting appropriate therapy and in determining drug doses, schedules, and dose modifications. The treating physician or other health care provider is responsible for determining the best treatment for the patient. ASCO and *JCO* assume no responsibility for any injury or damage to persons or property arising out of the use of these protocol materials or due to any errors or omissions. Individuals seeking additional information about the protocol are encouraged to consult with the corresponding author directly.

YALE UNIVERSITY SCHOOL OF MEDICINE
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Research

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://info.med.yale.edu/hic/forms/index.html. Submit the original application and two (2) copies of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	
	DATE STAMPED-RECEIVED	PROTOCOL NUMBER 1012007780

Title of Research Project: Lifestyle, Exercise and Nutrition (LEAN) Study			
Principal Investigator: Melinda L. Irwin		**Yale Academic Appointment:** Associate Professor	
Campus Address: 60 College St, Room 428			
Campus Phone: 5-6392	**Fax:** 5-6279	**Pager:**	**E-mail:** Melinda.irwin@yale.edu
Protocol Correspondent Name & Address (*if different than PI***):**			
Campus Phone:	**Fax:**	**E-mail:**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ Yale Cancer Center
☐ Yale-New Haven Hospital
☐ PET Center
☐ YCCI/Church Street Research Unit (CSRU)
☒ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☒ Specify Other Yale Location: EPH Rm 428 and 55 Church St, Suite 801

b. External Location[s]:

☐ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☐ Veterans Affairs Hospital, West Haven
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☐ Other Locations, Specify:

c. Additional Required Documents *(check all that apply)*: ☐ N/A

☒ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☒ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☒ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. January 1, 2011 - December 30, 2016

3. **Targeted Enrollment:** What is the number of subjects

a. targeted for enrollment at Yale for this protocol? N = 100
b. expected to sign the consent form? N = 100
c. expected to complete some or all interventions for this protocol? N = 100

4. **Research Type/Phase: (Check all that apply)**

a. **Study Type**

☒ Single Center Study
☐ Multi-Center Study
Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☐
☐ Coordinating Center/Data Management
☐ Other:

b. **Study Phase** ☐ **N/A**

☐ Pilot ☐ Phase I ☐ Phase II ☒ Phase III ☐ Phase IV
☐ Other (*Specify)*

c. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☐ Clinical Research: Patient-Oriented
☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 (“Bench-to-Bedside”)
☐ Translational Research #2 (“Bedside-to-Community”)
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

5. Is this study required to be registered in a public database? Yes ☐ No ☒

If yes, where is it registered?

Clinical Trials.gov registry ☒

Other (*Specify*)

6. Will this research study utilize clinical care services at Yale New Haven Hospital or YMG?

Yes ☐ No ☒

If yes, might these be billable to the subject, the sponsor, grant or other third party payer?

Yes ☐ No ☐

If you answered "yes", please register this study in the IDX/GE system at

http://www.yalemedicalgroup.org/pfs/forms/10000/NewStudyRequest.pdf

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate the funding source(s) for this study. Check all boxes that apply.

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Melinda L. Irwin	Telephone vs. in-person weight loss counseling on weight, body fat, and serum hormones breast cancer survivors	AICR	☐ Internal ☒ External	☒ Grant-M# ☐ Contract#

2. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

	Name	Signature ***	Protocol-Related COI?	Affiliation
Principal Investigator	Melinda L. Irwin		☐ Yes ☒ No	Yale
Role: Project Director	Maura Harrigan		☐ Yes ☒ No	Yale
Co-Investigator	Brenda Cartmel		☐ Yes ☒ No	Yale
Co-Investigator	Marianna Rothbard		☐ Yes ☒ No	Yale
Co-Investigator	Cary Gross		☐ Yes ☒ No	Yale
Research Assistant	Yang Zhou		☐ Yes ☒ No	Yale
Research Assistant	Lindsey Smith		☐ Yes ☒ No	Yale
Research Assistant	Michelle Baglia		☐ Yes ☒ No	Yale

***My signature here indicates that I have read, am in compliance with, and will continue to be in compliance with the HIC's Protocol-Specific Conflict of Interest policy and the University's policy on Conflict of Interest and Conflict of Commitment.**

NOTE: The HIC will remove from the protocol any personnel who have not signed the application and/or completed required training. A personnel protocol amendment will need to be submitted when training is complete or signature is provided.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?
☐ Yes, and I agree to submit the Protocol-Specific Conflict of Interest Disclosure Form.
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to submit a Protocol-Specific Conflict of Interest Disclosure Form if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and had the support of the hospital for this research project.

YNHH HSPA Name (PRINT) and Signature _____ Date _____

For HIC Use Only

Date Approved _____ **Human Investigation Committee Signature** _____

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Specific Aims

The specific aims of this study are to determine the efficacy and cost-effectiveness of a telephone-based weight loss program compared with an in-person weight loss program and usual care (control) treatment on 6-month changes in body weight, body fat, and serum hormones associated with prognosis in breast cancer survivors. Specifically, we will conduct a three-arm randomized controlled trial of 6-months of weight loss counseling (i.e., dietary-induced caloric restriction and physical activity) on clinically meaningful endpoints in 120 breast cancer survivors. The three arms will be:

1. In-person counseling
2. Telephone-based counseling
3. Usual care

The primary endpoints will be:

1. Change in weight, BMI, and percentage body fat from baseline to 6 months
2. Change in serum hormones from baseline to 6 months including fasting insulin, IGF-1, leptin, adiponectin, and C-reactive protein
3. Cost-effectiveness of each approach

The secondary endpoint will be:

1. Maintenance of weight loss at 12-months post randomization.
2. Assessment of skin carotenoids by use of resonance RAMAN spectroscopy (RRS).

We hypothesize that 6-month changes in body weight, fat, and serum hormones using the telephone will be similar to in-person counseling, but that the telephone-based approach will be more cost-effective. Results from this study will be novel in their own right, but will also provide strong preliminary data for a large-scale weight loss trial on disease-free survival where we would like to propose telephone-based counseling, yet first need to show its effectiveness in regards to amount of weight loss, costs associated with the intervention, and that we can reach more women via phone than in-person counseling. The ultimate goal is to get health insurance companies to reimburse for lifestyle/behavior change counseling after a cancer diagnosis so that weight loss treatment may be more accessible to the growing number of cancer survivors. Strengths of our study include our experience in conducting in-person and telephone-based exercise trials in breast cancer survivors; thus, we have the personnel, resources, and facilities in place and ready to go with little start up time necessary. Other strengths include the novel study design and potential for very clinically meaningful findings.

In summary, although behavioral programs involving weekly in-person clinic visits are the most effective treatments available for obesity, some adults would prefer to lose weight without having to participate in a structured face-to-face treatment program. Furthermore, the escalating obesity epidemic has prompted healthcare professionals to seek interventions that can reach large numbers of individuals in a timely and cost-effective manner. The telephone may offer obvious solutions for overweight women diagnosed with breast cancer. Lastly, few studies have examined the effect of weight loss on biological markers associated with prognosis. If we show a beneficial effect of weight loss on serum hormones known to be associated with recurrence and death, then more weight loss programs that are reimbursable may be made available to cancer survivors.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Background and Significance

Obesity, Physical Inactivity, and Breast Cancer Prognosis

Obesity and a sedentary lifestyle are associated with poor outcomes in women with breast cancer (1-6). Studies have shown that women who are overweight at the time of breast cancer diagnosis have up to a 2-fold increase in risk of recurrence as compared to lighter women (1-3), and physical inactivity after cancer diagnosis has been associated with a significant increase in breast cancer recurrence and death in women with breast cancer (4-6). Recent trials have demonstrated that in-person diet and exercise interventions can be successfully implemented during and after breast cancer treatment, and that breast cancer survivors who make changes in diet and exercise experience many quality of life and fitness benefits (7-10).

Weight Loss Treatments

Despite the major health significance of obesity, oncologists and health care providers have few obesity management options. Current pharmacological treatments are only modestly effective relative to cost, and bariatric surgery is not appropriate for many patients and prohibitively expensive as a public health strategy. Thus, the current "gold standard" approach involves intensive behavioral treatment with weekly face-to-face counseling (11,12). Specifically, effective weight loss treatment uses a combination of reduced caloric intake, increased physical activity and behavioral therapy. The successful Diabetes Prevention Program behavioral weight loss program, which produced a 58% reduction in diabetes incidence after 2.8 yrs, involved substantial individual in-person counseling, resulting in an average weight loss of 8% within three months of treatment (11). The impact of the Diabetes Prevention Program has made dissemination of behavioral weight loss programs for other disease outcomes, including breast cancer, a priority. Other behavioral weight loss trials that have used the Diabetes Prevention Program have also observed similar weight losses within just three to four months of initiating treatment (12,13).

However, the major drawback to this intensive behavioral treatment is the multiple in-person contacts which may be too expensive for widespread use. Further, some individuals may perceive attending these sessions as a burden, possibly limiting program participation. Thus, this approach to obesity treatment may be impractical to treat the large number of at-risk individuals as well as the growing population of breast cancer survivors. Thus, developing effective weight loss programs that are cost-effective and widely accessible is a health care priority, given that more than 50% of breast cancer survivors are overweight or obese and that weight loss is recommended to improve prognosis (14).

Alternative Methods for Delivering Weight Loss Treatments

To accommodate the needs of breast cancer survivors and to make obesity treatment more accessible, alternative methods for delivering weight loss programs are necessary. Telephone-based weight loss counseling may be a viable alternative to expensive in-person clinic visits. Being able to access information and services from the comforts of home reduces barriers that may significantly hinder a patient from receiving necessary care. Delays in seeking in-person treatment may stem from several concerns such as lack of time and lack of nearby services. Telephone-based treatments offer a novel solution to these problems. Furthermore, the

lack of in-person interaction may reduce social desirability and pressure for a patient to respond in a particular way (15).

The telephone has increasingly been used to provide behavioral change interventions, and several studies have demonstrated its potential for delivering weight loss treatment in healthy men and women (15); however, few, if any, studies, and no studies in cancer survivors, have directly compared telephone to in-person weight loss treatment. However, while a major advantage of the telephone-based approach lies in the ability to widely disseminate them much more inexpensively than traditional in-person therapies, a disadvantage of this approach is the potential ease with which participants may disengage; it may be much easier not to keep an appointment with a telephone-based weight loss counselor than an in-person counselor. Thus, whether counseling by telephone is as effective as in person counseling is unknown. If we are able to show that a telephone approach to weight loss is as effective as in person counseling, then weight loss treatment may be more accessible and cost-effective to the growing number of breast cancer survivors.

Over the course of the study skin carotenoids will be measured. During weight loss carotenoid status of an individual may change because of a change in diet (increase in fruit and vegetable intake) or/and because carotenoids, which are sequestered in fat, may be released increasing the levels in the body. Change in carotenoid status may provide a mechanism of providing feedback to those on a healthy weight loss program to motivate compliance with the program.

3. **Research Plan:** Provide an orderly scientific description of the study design and research procedures as they directly affect the subjects.

Design overview: We propose to examine efficacy and cost-effectiveness of two different behavioral weight loss approaches compared with usual care on weight, body fat and serum hormones in 100 breast cancer survivors. Women will be recruited from the Yale New Haven Hospital Tumor Registry. In addition, participants who were screened for another ongoing trial (the HOPE Study, HIC # 0906005623) and previous studies (Yale Exercise and Survivorship Study, HIC #14476 and IMPACT Study, HIC # 25390) who were ineligible or not interested, but consented to being contacted for other studies will also be approached for interest and eligibility in the proposed study. The two weight loss interventions will be based on the Diabetes Prevention Program. We will conduct baseline and 6-month clinic visits at Yale University.
Study Population: Inclusion criteria include overweight (BMI >= 25.0 kg/m^2) breast cancer survivors who have completed chemotherapy and/or radiation therapy. Women should be physically able to exercise (i.e., not using a cane or wheelchair and be able to walk for at least 10 min). They should agree to be randomly assigned to any of the three groups, and give informed consent to participate in all study activities. They should be accessible by telephone. Participants should read and communicate in English. Women are ineligible if they are pregnant or intending to become pregnant in the next three years, recent (past 6 months) stroke or myocardial infarction, or severe uncontrolled mental illness. Thus, the primary eligibility critieria are simply being overweight and willing to be randomized to any group. We chose not to include other eligibility criteria, e.g., time since diagnosis, because we want our results to be generalizable to most breast cancer survivors, and because being overweight negatively affects prognosis at any time (i.e. before diagnosis, at diagnosis, and years after diagnosis).
Recruitment: Recruitment will take place between month 2 and 18 of this two year study. To identify potential participants, we will use the Yale-New Haven Hospital Tumor Registry. This registry service provides the PI with the participants' names, addresses and telephone numbers, and their oncologist or surgeon's names. We will also contact women already screened for previous studies conducted by Dr. Melinda Irwin and for whom we have physician passive

consent to contact from the prior study (see above for specific studies). We will also screen women who call in to our study phone number.

For newly identified patients, physicians consent to contact their patients will be passive, that is the physician will be sent a list of women identified as potentially eligible for the study. If a physician has information about a specific patient regarding their participation in the study he/she will be asked to contact the office with this information. If we have had no response from the physician within 2 weeks of mailing the letter, we will mail an invitation letter to the participant, describing the study and telling her that a member of the study staff will be contacting her within a week to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, a baseline clinic visit will be scheduled for the next week. This recruitment approach was successfully used in our exercise trial in breast cancer survivors (8).

Our goal is to recruit 100 breast cancer survivors over one year. Approximately 300 women are diagnosed or treated with breast cancer per year at Yale-New Haven Hospital. However, time since diagnosis is not an eligibility criteria; thus, we will be able to approach more than 300 women (e.g., if just recruiting women diagnosed in the past 5 yrs, then we can approach 1500 women) to randomize 100 women. This rate suggests that our recruitment goal is feasible. We also propose to recruit a sample for this project that is at least 10% African-American and 10% Hispanic. This proportion of women from ethnic minority groups surpasses the proportion found in New Haven County. Using the hospital tumor registry, we will target the minority women early in order to maximize the percent of minority women in the final sample.

Data Collection: Data collection will occur between months 2 and 10 of the study. Data collection will involve a screening phone call, and baseline and 6-month clinic visit.

Screening Phone Call: Research staff will call participants within one week after they have received a study brochure. If the participant is interested, the research staff will administer over the phone an eligibility questionnaire. If the participant is eligible, a baseline clinic visit will be scheduled for the following week. The baseline questionnaires and food frequency questionnaire will be mailed to the participant for self administration, along with instructions regarding the baseline clinic visit.

Baseline Clinic Visit: Participants will be scheduled for a baseline clinic visit at Yale New Haven Hospital. Research staff will explain the study and then answer any questions. The participant will sign the informed consent form, and research staff will interview-administer several questionnaires and review the self administered questionnaires. Weight and height will then be measured. A DEXA scan and a RRS scan (see Measurements) will then be conducted. A 12-hour fasting blood sample will also be collected (see Measurements).

Randomization: Women will be randomized into one of 3 study arms using a random permuted block design. Research staff collecting body composition data, as well as reviewing forms and entering data, will be blinded to the participant's study group. After randomization, the project manager will call the participant to inform her of her group, and to schedule her next visit.

6-Month Visits: The same data that was collected at the baseline visit will be collected in a similar manner at the 6-month visit. Following the completion of the 6-month visit a letter will be mailed to participants informing them of a limited number of personal information from the study, including weight loss, body composition, steps walked per day and waist and hip circumference.

12-Month Follow Up: A mailed follow up will be conducted at 12-months post randomization. Questionnaires will be mailed to the participant with a pre-paid envelope for their return.

Baseline and Follow-up Measurements

Questionnaires: Information will be collected on medical history via a standard questionnaire. A screening questionnaire assessing eligibility and any comorbidities will also be administered.

Physical Activity: The 7-Day Daily Activity Log (7-Day DAL) will be the primary measure used to compare physical activity levels at baseline and 6-months among the three groups (16). All participants will complete the log for seven consecutive days, recording the

amount of time spent in moderate- to vigorous-intensity recreational exercise. We will calculate their total minutes per week of exercise. Participants randomized to in-person and telephone counseling will also complete the 7-day DAL weekly.

Secondary measures of physical activity will include completion of a physical activity questionnaire and pedometer log at both visits. Specifically, the physical activity questionnaire will assess their past six months of physical activity (17). Hours/week spent in different types (recreational, household, and occupation) and intensities (light, moderate, and vigorous-intensity) of activity will be computed over the past six months (18). Lastly, the Yamax pedometer will be used to measure steps walked per day for 7 days at baseline and 6-months (19). Women randomized to in-person or telephone counseling will also be encouraged to wear the pedometer throughout the six months of intervention. Participants will be given a form to record the number of steps walked/day. When she wakes in the morning, she will attach the pedometer to her belt or waistband and wear it for the entire day (except when bathing or sleeping). When she goes to bed at night, she will take the pedometer off and record steps walked. Average steps/day at the three time points will be compared among the three groups. We chose to use the pedometer rather than an accelerometer such as Actical because of cost ($10 vs. $500) and because the pedometer will be motivational during the intervention and provide feedback to the women as to how much walking they have done. All physical activity measures have been used successfully in our exercise trials in breast cancer survivors (8-10).

Dietary Intake: The endpoint measures of diet change will be mean, group level changes in daily caloric intake, based on a 120-item food frequency questionnaire (FFQ) which was developed for the Women's Health Initiative Study and has been validated against 4-Day Food Records and 24-hour Dietary Recalls (20). FFQs will be administered at baseline and 6-months. Participants randomized to the two interventions will also complete daily food records. While both the diet and physical activity assessments have been shown to be valid and reliable, they are not our primary outcome measure, but process measures. The primary outcome is body weight, which is measured objectively, in person, and with high accuracy and reliability.

Weight and Height: Weight and height will be measured by research staff blinded to the participant's randomization group at baseline and 6-months. Participants will be weighed in light indoor clothing, without shoes, rounding up to the nearest 0.1 kg; height will be measured in a standard manner, without shoes, using a stadiometer, rounding up to the nearest 0.1 cm. All measures will be performed and recorded twice in succession.

Waist and Hip: Waist and hip measures will be collected at baseline and 6-monhts. Participants will be measured with a cloth tape measure in light indoor clothing, rounding up to the nearest 0.1 cm. All measures will be performed and recorded twice in succession.

Dual Energy X-Ray Absorptiometry (DEXA) Scans: DEXA is the gold standard measure of assessing bone density, osteopenia, osteoporosis, and body fat (21). DEXA scans will be performed at baseline and 6-months. The DEXA measurements will be made with a Hologic scanner (Hologic 4500 with a "Discovery" upgrade, Hologic Inc, Waltham, Mass). A whole-body scan takes approximately 10 minutes to complete. We will measure percent body fat, LBM (kg), bone area (cm^2), and bone mineral density (g/cm^2). All DEXA scans will be evaluated by a clinical assistant who will be blinded to the intervention group.

Resonance RAMAN Spectroscopy (RRS): RRS is a quick novel noninvasive method of assessing skin carotenoids. The methodology had been validated in at prior study at Yale (HIC: 0303025070, PI: Dr. Susan Mayne;(26)). Briefly, a small scanner which shines blue light is placed on the palm of the hand for 30 seconds. The palm is cleaned with an alcohol wipe prior to the scan, A RRS reading is available after a further 30 seconds. The procedure is repeated at the same body location. Skin color is self assessed by the participants at the baseline visit using samples that are used in plastic surgery to assess skin color. Melanin content (skin color) may have a small effect on RRS, but this effect is minimized by assessing skin carotenoids in the

palm, which has a lower melanin content than other body sites.

Blood Draw and Serum Hormones: Fasting blood (> 12 hours) will be drawn at baseline and 6-months in a standardized fashion. Two 10-ml red-top tubes will be collected for serum, and a 10-ml light blue-top and 10-ml lavender-top will be collected for citrate and EDTA plasma. Technicians in the lab will centrifuge the samples at 2,000 rpm for 15 minutes at 4°C. Plasma and buffy coat will be separated and transferred into cryovials and labeled with freezer-proof labels with participant ID #s and date (no identifiers will be included). All specimens collected will be stored temporarily at 4 degrees C during transportation or priot to delivery to the YCCI specimen storage facility, and then stored at -70 degrees C until it is time to analyze them. All the hormones to be measured (insulin, IGF-1, leptin, adiponectin and C-reactive protein) have been previously measured in our lab and published. We will use immunoassay techniques and kits from Diagnostic Products Corporation (DPC, Los Angeles, CA) to measure each hormone value. Each woman's baseline and follow-up samples will be used in the same batch, and an equal number of intervention and control samples will also be included in the same batch. Blind duplicates are also included in and between batches to estimate coefficient of variations.

Quality of Life (QOL): QOL will be self-reported and collected at the baseline and 6-months. The Functional Assessment of Cancer Therapy-Breast (FACT-B) and Fatigue questionnaire will be administered to assess overall quality of life (22). The FACT-B and FACT-F measures physical, emotional, social, and functional well-being as well as quality of life issues specific to breast cancer survivors such as fatigue. QOL is not a primary outcome, but we will explore the effect of each intervention on QOL to inform us for future studies.

Psychological outcomes: Validated measures will be used to assess the psychological outcomes at baseline, 6- and 12-months. **Self-efficacy** will be assessed using the Rosenberg Scale [80]. The scale was shown to be reliable in the Yale Exercise and Survivorship (YES) Study, with Cronbach's alpha of .91. **Depression** will be measured with the Centers for Epidemiological Studies Depression Scale [81] (CES-D). Cronbach's alpha was .87 for the YES Study. **Anxiety** will be measured using the 20-item State-Trait Anxiety Index [82] (STAI), which differentiates between transient anxiety ("state anxiety") and more long-standing anxiety ("trait anxiety"). Participants in the study will complete only the state anxiety scale (STAI-YI) as trait anxiety is not expected to be modifiable. Chronbach's alpha was .94 in the YES Study.

Theory of Planned Behavior: Prior to randomization, information on intention, attitude, perceived behavior control, and subjective norm will be collected via reliable and valid questionnaires drawn from Ajzen's Theory of Planned Behavior (23).

Transtheoretical Model: Prior to randomization, participants will complete the Transtheoretical Model Stages of Change questionnaire for diet and exercise (24). We will be able to tailor the intervention to each participant's baseline stage of change.

Medical Record Abstraction and Physician Verification of Treatment Reports: The following will be abstracted from medical records: disease stage, hormone receptor status, HER-2 neu status, surgery, therapy and evidence of completion.

Weight Loss Intervention: The in-person and telephone interventions will be based on the Diabetes Prevention Program weight loss program, which uses a combination of reduced caloric intake, increased physical activity, and behavior therapy (11). The content of the weight loss program will be similar for the in-person and telephone interventions, but the approach will vary (i.e., in-person vs. telephone counseling). The weight loss intervention will be conducted by a Registered Dietitian, who has training in exercise physiology and behavior modification.

During the 6-month intervention, participants will receive weekly (month 1), then bi-weekly (months 2 and 3), then monthly (months 4, 5, and 6) individualized counseling sessions. An advantage of tapering the frequency of visits from weekly to every other week and then monthly works as a process tool to help transfer the work or responsibility onto the participant for life long change and maintenance of behavior change. The 11 sessions represent a core

curriculum, with general information about diet and behavior strategies such as self-monitoring, goal setting, stimulus control, problem solving, and relapse prevention training. Standard scripts and educational handouts will be used to ensure comparability of weight loss counseling among the two approaches. Sessions will focus on strategies for adopting eating and exercise behaviors for weight loss and will be based on constructs of social-cognitive theory. Each session typically introduces one or two new topics in behavioral weight control, including recording food intake and physical activity, eating at regular times, portion control, limiting times and places of eating, and coping with negative thoughts related to overeating. All topics are accompanied by a homework assignment. Of these, recording daily food intake and physical activity are the most important. Weight is also measured weekly to provide feedback on adherence and to increase motivation.

The goal of the two interventions is for individuals to achieve and maintain a loss of 10% initial body weight (this was the individual weight loss goal in the Diabetes Prevention Program, and it was achieved within 6 months). Weekly and average weight losses will be compared with expected weight losses corresponding to the week in the program. To achieve this weight loss, participants will be instructed to reduce energy intake to the range of 1200 to 2000 kcal/d based upon baseline weight and dietary fat to $\leq$ 25% of total energy intake. The diet intervention includes extensive teaching about how to achieve the goal calorie reduction. This teaching includes setting a calorie goal, setting a fat gram goal, calorie counts of foods, how to self-monitor, and coping with challenges to eating behavior changes. Several tools are provided in the DPP, such as graphs for monitoring weight, cooking and shopping for lower-fat eating, etc. Reported calories will be compared with individualized goals.

The physical activity program relies heavily on home-based exercise. This approach was used in the Diabetes Prevention Program and has been used successfully in two of our exercise trials. Although walking is encouraged, participants will be allowed to choose other types of moderate-intensity exercise. The training program will start at 40% of maximal heart rate for 20 min/session and gradually increase to 60 - 80% of maximal heart rate for 30 min/session by week 4, where it will be maintained for the duration of the study. Thus, the exercise goal is 150 min per week (e.g., three-50-min sessions per week or five-30-min sessions per week). The number of minutes spent participating in physical activity will be compared with the weekly goal. Lastly, participants will also be encouraged to increase their lifestyle physical activity through activities of daily living such as using stairs rather than elevators.

In-Person Weight Loss Counseling: Participants randomized to in-person counseling will meet weekly for month 1, then every other week for months 2, and 3, and then monthly for months 4-6 at Yale University. The meetings will last 30 minutes. Participants will turn in their diet and exercise logs and also be weighed. A lesson will then be discussed (see above for content).

Telephone-based Weight Loss Counseling: The exact same information, content, schedule, and 30 minute sessions will be provided to telephone-based participants as offered to participants who receive in-person counseling. Participants will be taught diet, exercise and behavior change strategies via the telephone (weekly calls for month 1, every other week for months 2-3, and monthly for months 4-6). All lessons and diet and physical activity logs will be mailed to them at the beginning of the program. Participants will record their daily diet and exercise in the logs. Every four weeks, participants will return, via stamped, addressed envelopes, the logs to the study office. During the phone calls, the counselor will ask the participant to weigh herself on the scale provided to the participant and record it on the weight log (as well as report it to the counselor). If the participant is not available during the regularly scheduled time to talk, the counselor will make additional phone call attempts later that day or the next day. The counselor will document any missed calls and number of attempts to contact the participant. The telephone approach we are using is based on our successful telephone-administered exercise trial among newly diagnosed breast cancer patients (25).

Usual Care Group: Immediately after randomization, participants in the Usual Care Group will be provided written information that emphasizes the importance of a healthy lifestyle. Usual care participants will be encouraged to follow the ACS nutrition and physical activity guidelines. Upon completion of the study (at 6 months), usual care participants will be offered all the educational material, as well as an in-person or telephone counseling session.

Statistical Analyses: Participants will be grouped according to the intention-to-treat philosophy in which all randomized participants will be grouped according to their intervention assignment at randomization, regardless of compliance or adherence to the study. We will perform Analysis of Covariance, with each woman's change in weight, body fat, and hormone modeled as a function of treatment with a covariate included for the baseline value. Age, menopausal status, race/ethnicity, disease stage, adjuvant treatment, hormonal therapy use, time since diagnosis, and time since completing adjuvant treatment will be examined as potential covariates to be included in multi-variable adjusted analyses. We will also analyze certain process variables to determine dose-response effects. Specifically, we will examine attendance to in-person visits and telephone calls; number of weekly diet and exercise logs submitted; weekly adherence to diet and exercise goals; and compliance to follow-up visits. Lastly, a cost-effectiveness analysis will be completed. Counseling costs will be derived from time spent in encounters between the participant and counselor and the salary of the counselor employed. A time estimate will be attached to each encounter call and total counseling time per participant over the 6-months will be computed. An average counseling time for each intervention type will then be computed. The usual care group will be assigned zero on this component since the educational handouts utilized by this group have already been developed by AICR, NCI, and ACS. Overhead costs include the operating cost of office space rental and phone charges. A cost-effectiveness ratio will be computed for each group to provide a measure of how efficiently the interventions produced a kilogram of weight loss.

Power and Sample Size Considerations: Based on a 10% weight loss (e.g., 8 kg loss in an 80-kg woman) and SD of 12 kg, we would need to randomize 35 women per group (105 in total) to have 80% power to detect statistically significant weight differences between groups (10). Enrolling 33 per group (10 in total) will provide enough power to observe statistically significant findings even if 5 women per group are not compliant.

Data Processing, Storage, and Confidentiality: We will use a clinical study data management system that is located on a secure server at Yale University to store and manage study data. Only Dr. Irwin and her staff will have access to the database. Access will be password protected.

Quality Assurance: Specific Quality Assurance procedures will include: 1) Development of and continuous updating of a detailed protocol and procedures manual; 2) Careful and systematic training of staff on performance of clinic measures, interviewing, and other procedures; 3) Range and consistency checks on data collection forms. All staff collecting data will be instructed to be conversant with the study's protocol and all intervention manuals.

Study Timeline: The first two months of funding will involve obtaining IRB approval, finalizing the study protocol, and beginning recruitment. During months 2 through 18, we will randomize ~7 women per month to one of the three groups and follow them for 6-months. The last participant will complete the 6-month intervention in month 24. A mailed follow up will be conducted at 12-months post randomization.

Strengths and Limitations: We believe that the proposed study will provide clinically meaningful information on the effect of two different interventions on weight loss, body fat, and biological markers of prognosis in breast cancer survivors, and will help guide the incorporation of weight loss counseling into breast cancer treatment. Study strengths include our strong preliminary experience of conducting in-person and telephone-based exercise interventions in breast cancer survivors with high adherence and compliance rates. Given our preliminary experience and other studies in progress, we have the personnel, resources, and facilities in place

and ready to go with little start up time necessary. Other strengths include the novel study design and potentially clinically meaningful findings.

SECTION VI: RESEARCH INVOLVING DRUGS, DEVICES, BIOLOGICS & PLACEBOS

1. **Identification of Drug, Device or Biologic:** What is (are) the **name(s)** of the drug(s), device(s) or biologic(s) being used? Identify whether FDA approval has been granted and for what indication(s).

   Not applicable.

   All protocols which utilize a drug, device or biologic **not** approved by, but regulated by, the FDA must provide the following information: ☒ **Not applicable to this research project**

   i. What is the Investigational New Drug (IND) or Investigational Device Exemption (IDE) **number** assigned by the FDA?

   ii. For IDE's: Did the FDA approve this IDE as a Category A (experimental/investigational) or as a Category B (non-experimental/investigational)?

   iii. Who holds the IND or IDE?

   The clinical investigation of a drug product that is lawfully marketed in the United States may be exempt from the requirements for filing an IND. If there is no IND and an exemption is being sought, complete the following:

   i. Is the intention of the investigation to report to the FDA as a well controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug? ☐ Yes ☐ No
   ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, is the intention of the investigation to support a significant change in the advertising for the product? ☐ Yes ☐ No
   iii. Does the investigation involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product? ☐ Yes ☐ No
   iv. Will the investigation be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56)? ☐ Yes ☐ No
   v. Will the investigation be conducted in compliance with the requirements regarding promotion and charging for investigational drugs? ☐ Yes ☐ No

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

3. **Source:** a) Identify the source of the drug, device or biologic to be used.

   b) Is the drug or device provided free of charge? ☐ Yes ☐ No
   If yes, by whom?

4. **Preparation and Use:** Describe the method of preparation, storage, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

5. **Use of Placebo:** ☐ **Not applicable to this research project**
   Provide a justification which addresses the following:
   a. Describe the safety and efficacy of other available therapies (if any).
   b. State the maximum total length of time a participant may receive placebo while on the study.
   c. Address the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset.)
   d. Describe the procedures that are in place to safeguard participants receiving placebo.

6. **Use of Controlled Substances:**
   Will this research project involve the use of controlled substances in human subjects?
   ☐ Yes ☐ No See instructions to view controlled substance listings.

   If yes, is the use of the controlled substance considered:
   ☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
   ☐ Non Therapeutic: Note, the use of a controlled substance in a non therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**
   Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended? ☐ Yes ☐ No
   If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

SECTION VII: HUMAN SUBJECTS

1. **Recruitment Procedures:** How will potential subjects be identified, contacted and recruited? Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☒ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☒ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ Other (describe):	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	

Recruitment will occur at Yale University and will take up to 1.5 years to complete. To identify potential participants, we will use the Yale-New Haven Hospital Tumor Registry. This registry service provides the PI with the participants' names, addresses and telephone numbers, and their oncologist or surgeon's names. We will also contact women already screened for previous studies conducted by Dr. Melinda Irwin and for whom we have physician passive consent to contact from the prior study (see above for specific studies). We will also screen women who call in to our study phone number. For newly identified patients, physicians consent to contact their patients will be passive, that is the physician will be sent a list of women identified as potentially eligible for the study. If a physician has information about a specific patient regarding their participation in the study he/she will be asked to contact the office with this information. If we have had no response from the physician within 2 weeks of mailing the letter, we will mail an invitation letter to the participant, describing the study and telling her that a member of the study staff will be contacting her within a week to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, a baseline clinic visit will be scheduled for

the next week. This recruitment approach was successfully used in our exercise trial in breast cancer survivors (8).

1.a. **Assessment of Current Health Provider Relationship for HIPAA Consideration:** Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No
If yes, describe the nature of this relationship.

2. **Subject Population** Provide a detailed description of the targeted involvement of human subjects for this research project.

For this trial, women diagnosed with Stage I-III breast cancer who are overweight (BMI $\geq$ 25 kg/m2) will be recruited to participate in a weight loss trial on body composition and serum hormones. Women will have completed surgery and adjuvant treatment (i.e., radiation and/or chemotherapy), physically able to exercise, English speaking and accessible via telephone.

3. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion? How will eligibility be determined, and by whom?

3.a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☐ No

3.b. If yes, will identifiable health information be collected during this screening process and retained by the research team? ☒ Yes ☐ No

Table D.1: Study Inclusion and Exclusion Criteria
Inclusion Criteria:

- Ages 18 to 75 years
- AJCC Stages 0-IIIC Breast Cancer
- BMI ≥ 25 kg/m2
- Completed surgery, chemotherapy and radiation at least 2 months ago
- Physically able to exercise
- Agrees to be randomly assigned to either weight loss or control
- Gives informed consent to participate in all study activities
- Able to come for baseline and 6-month clinic visits
- Mentally competent

4. **Subject Classifications: Check off all classifications of subjects that will be invited to enroll in the research project.** Will subjects, who may require additional safeguards or other considerations, be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
	☐ Students	☒ Females of childbearing potential

a. Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

SECTION VIII: CONSENT/ ASSENT PROCEDURES

1. **Consent Personnel:** List all members of the research team who will be obtaining consent/assent.

   Melinda L. Irwin and study staff.

2. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   Women identified at the Yale Tumor Registry

   We will mail an invitation letter to the participant, describing the study and telling her that a member of the research team will be contacting her within one week to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, a baseline visit appointment will be scheduled for the next week at Yale New Haven Hospital. At the visit, the study will be described in detail again. If the participant is interested in participating and eligible, she will read and sign the informed consent form.

   Women who were identified for prior studies and agreed to be recontacted regarding other research studies
   We will call women to determine if interested and eligible for the study described in this protocol. If the participant is eligible and interested, a baseline visit appointment will be scheduled for the next week at Yale New Haven Hospital. At the visit, the study will be described in detail again. If the participant is interested in participating and eligible, she will read and sign the informed consent form.

3. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   First, the participant's physician will provide us with consent to contact his/her patient for participation in the study, unless prior physician consent was obtained to contact the patient for Dr. Irwin's other studies. Second, we will conduct a screening phone call to determine interest and eligibility. Third, we will meet them in person to further discuss the study and determine interest and eligibility. During the screening phone call and in-person baseline visit, we will ask open-ended questions about the research to determine whether the participant understands what is being explained to her. Such questions include: "Can you tell me what will happen if you agree to take part in this study?" "How will this study help you?" and "What should you do if you want to stop being in this study?"

4. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

   We have attached a copy of our adult compound authorization form.

5. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use.

   Only English-speaking subjects will be eligible to participate in the study.

6. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:

☒ **This section is not applicable to this research project**

Waiver of consent: (No consent form from subjects will be obtained.)

a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

Waiver of **signed** consent: (Verbal consent from subjects will be obtained.)

☒ **This section is not applicable to this research project**

a. Would the signed consent form be the only record linking the subject and the research? ☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ☐ No **AND**
d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☒ Compound Consent and Authorization form
☐ HIPAA Research Authorization Form

8. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only)

Choose one: For entire study: _____ For recruitment purposes only: __x____

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;

We are requesting a waiver of HIPAA authorization for recruitment purposes and to collect PHI information from clinicians. The YNHH Tumor Registry will provide us with the names and contact information of women diagnosed with breast cancer in CT between years 2006-2012. We will use this information to contact the patient's clinician to get consent to contact the patient. We will then contact the patient (via recruitment letter) to determine interest in participating in our study.

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by

subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

1. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Assessment of the risk associated with participating in the study can be categorized as ***minimal***. The nutritionist/counselor will have weekly/monthly contact with each participant randomized to the weight loss group. During this time, the counselor will inquire about each participant's overall health and how she is adapting to the weight loss program.

Risks associated with the blood draw are minimal. There is a small risk of bleeding, bruising, or discomfort at the site of the blood collection. Attention will be taken to apply pressure following the procedure to reduce bleeding. Occasionally a patient may feel dizzy when blood is being withdrawn. The participant will be asked to lie down for a few minutes until the dizziness passes. The blood draw will occur at YCCI following their protocol. The YCCI uses only skilled technicians and nurses for blood sampling.

Risk associated with the DEXA scan is minimal. A DEXA scan x-ray involves exposure to radiation. Although it can vary from person to person, the whole-body radiation exposure from each scan will be about 2.5 mrem. The total exposure for the study will be a small fraction of the average annual exposure a person in the United States receives from natural background radiation. The risk of harm from this amount of radiation is low and no harmful health effects are expected. The DEXA scan will occur at Yale YCCI following their protocol.

There are no known risks associated with the RRS scan. Both the operator and the participants will wear protective eye wear (goggles) to protect against any extraneous light from the scanner head. Participants will be asked to remove metal bracelets to eliminate the possibility of light being reflected from the metal during the scan.

It is unlikely that participants will incur injury as a result of participation in this research. However, if a participant is injured as a result of her participation in the study, treatment will be provided. The participant or her insurance carrier will be expected to pay the costs of this treatment.

There is also a small possibility that personal information may become know to a person not involved in the study. We will take several precautions to protect confidential information. All data will be stored on a database that will be stored on a Yale University secure server. Files that contain names and other identifying information will be kept separately from interview data where study ID numbers are used. As always, no subject will ever be identified by name or other identifying information.

Lastly, all staff have or will have taken the Human Investigations Training Course either online (through NIH) or in person through the Yale University School of Medicine. Dr. Melinda Irwin (Principal Investigator) will conduct data and safety reviews every six months. She will evaluate the frequency and severity of any adverse events and determine if modifications to the protocol or consent form are required. A summary of the adverse events will be reported to the HIC every 12 months.

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Please see above.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
    c. Data and Safety Monitoring Plan:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency [*e.g.,* every six months]. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment.

Either the principal investigator, the Human Investigation Committee (HIC), Yale Cancer Center, YCCI, QUACS, or NCI have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and adverse events or other problems are not anticipated. However, any serious (i.e. that requires medical attention) and unanticipated adverse events that are related or possibly related to the study or unanticipated problems involving risks to subjects or others will be reported in writing, within 48 hours of the study staff becoming aware of the event, to the HIC and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all adverse events that occur during the conduct of this research project via email and regular weekly staff meetings. She will conduct data and safety reviews every six months. She will evaluate the frequency and severity of any adverse events and determine if modifications to the protocol or consent form are required. A summary of any serious and unanticipated adverse events that are related or possibly related to the study or unanticipated problems will be reported to the HIC every 12 months. The protocol's research monitors including the Yale Cancer Center, the Yale Center for Clinical Investigation Research Subject Advocates (YCCI RSAs), Cancer Center Protocol Review Committee (PRC), and AICR will be informed of serious and unanticipated and related adverse events (e.g., increased risk of recurrence or death resulting from exercise) within 5 days of the event becoming known to the principal investigator.

4. **Confidentiality & Security of Data:**

a. What protected health information about subjects will be collected and used for the research?

Names and contact information (address, telephone number and email address) will be collected, but not used for research. This information will only be used to contact the participant for study participation, and then once enrolled, information will be used to contact the participant if she is missing an appointment. Date of diagnosis of breast cancer and date of birth will also be collected. However, we will take several precautions to protect confidential information. All data will be stored on a database located on a password-protected secure server that is accessible only to the PI and her research team.

b. How will the research data be collected, recorded and stored?

Data will be collected on forms that will then be data entered and stored on a password protected database located on a Yale secure server that is accessible only to the PI and her research team. Data Entry Security: Users can only gain access to the database through authorization by the Principal Investigator of specific privileges for a specific study.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☒ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during the subject participation in the study?

Data will be stored on password-protected database on a secure server accessible only to the PI and her research team. Digital data, used for data analysis, will be stored on CD and desktop computer that are password protected. All hard copies of questionnaires and forms will be filed in locked file cabinets in the PI's locked office.

e. What mechanisms are in place to ensure the proper use and continued protection of these data after the subject participation in the study has ceased?

After the subject has completed the study, all hard copies of questionnaires and forms and all digital data will be filed in locked cabinets or password-protected database on a secure server.

f. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Ten years after the end of the study, all identifiable data will be destroyed by the PI. Hard copies will be shredded and digital data will be deleted from computers and CDs.

g. Who will have access to the protected health information? (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, QUACS, SSC, etc.)

Only the PI and her research staff will have access to the protected health information.

h. Which external or internal individuals or agencies (such as the study sponsor, FDA, QUACS,
SSC, etc.) will have access to the study data?

Only the PI and her research staff will have access to the study data. If AICR, YCC, or YCCI requests to see the data, they may do so.

i. If appropriate, has a Certificate of Confidentiality been obtained?

N/A

j Are there any mandatory reporting requirements? (Incidents of child abuse, elderly abuse, communicable diseases, etc.)

N/A

5. **Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The potential benefit of this study is the provision of new knowledge about how weight loss among overweight and obese breast cancer survivors may affect breast cancer prognosis. Collection of weight loss, diet and physical activity patterns and effect on breast cancer

biomarkers should provide information for cancer surgeons and oncologists, and physicians to help cancer survivors manage their survivorship. The benefits to the participants include better knowledge of changes in their weight, diet and physical activity habits, and an improvement in their cardiovascular risk, improved body composition and quality of life, and possibly a decreased risk of death.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

An alternative is not participating in the study.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects and the conditions for receiving this compensation.

Women randomized to weight loss will be given a digital scale and measuring cups to keep (value $50). All women will receive a pedometer to keep (value $20). The costs for all study tests and procedures, including DEXA scans and blood analysis will be provided free of charge. Parking costs for the baseline and 6-month clinic visit will be paid for by the study.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

There is no cost associated with participation in this study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

It is unlikely that a participant will incur injury as a result of participation in this research. Should an injury associated with the study occur, treatment will be provided. The participant's insurance carrier will be expected to pay the costs of the treatment.

LITERATURE CITED:

1. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin. 2006 Nov-Dec;56(6):323-53.
2. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. The New England Journal of Medicine. 2003;348(17):1625-38.
3. Kroenke CH, Chen WY, Rosner B, Holmes MD. Weight, weight gain, and survival after breast cancer diagnosis. J Clin Oncol. 2005 Mar 1;23(7):1370-8.
4. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005 May 25;293(20):2479-86.

5. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2008 Feb;17(2):379-86.
6. Irwin ML. Influence of pre- and post-diagnosis physical activity on survival in breast cancer survivors: the Health, Eating, Activity, and Lifestyle (HEAL) Study. Journal of Clinical Oncology. 2008; 26(24):1-7.
7. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: cardiopulmonary and quality of life outcomes. J Clin Oncol. 2003 May 1;21(9):1660-8.
8. Irwin ML, Cadmus L, Alvarez-Reeves M, et al. Recruiting and retaining breast cancer survivors into a randomized controlled exercise trial: The Yale Exercise and Survivorship Study. Cancer, 2008 Jun 1;112(11 Suppl):2593-606.
9. Irwin ML. Randomized controlled trial of exercise on insulin and IGFs in breast cancer survivors. Cancer, Epidemiology, Biomarkers, Prevention 2009; 18(1): 306-13.
10. Irwin ML. Randomized controlled trial of exercise on body fat, lean mass, and bone mineral density in breast cancer survivors. Obesity. 2009. 17(8):1534-41.
11. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393-403.
12. Brownell K, Heckerman C, Westlake R. Therapist and group contact as variables in the behavioral treatment of obesity. J Consult Clin Psychol 1978; 46: 593-94.
13. Wing R. Behavioral weight control. In: Wadden T, Stunkard A, eds. Handbook of obesity treatment. New York, NY: Guilford Press; 2002, pp. 301-16.
14. Irwin ML, McTiernan A, Baumgartner R, et al. Changes in body fat and weight after a breast cancer diagnosis: Influence of demographic, prognostic and lifestyle factors. Journal of Clinical Oncology, 2005; 23(4): 774-82.
15. Jeffery RW, Sherwood NE, Brelje K, et al. Mail and phone interventions for weight loss in a managed-care setting: Weigh-to-be one-year outcomes. International J of Obesity 2003; 27: 1584-92.
16. Blair S, Haskell W, Ho P, et al. Assessment of habitual physical activity by a Seven-Day Recall in a community survey and controlled experiments. Am J Epidemiol 1985; 122: 794-804.
17. Kriska A. Modifiable activity questionnaire. Med Sci Sports Exer 29; S73-78: 1997.
18. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Schmitz KH, Emplaincourt PO, Jacobs DR, Leon AS. Compendium of physical activities: An update of activity codes and MET intensities. Medicine and Science in Sports and Exercise 2000; 32(9): S498-S516.
19. Bassett D, Ainsworth B, Leggett S, et al. Accuracy of five electronic pedometers for measuring distance walked. Med Sci Sport Exer 1996; 28: 1071-7.
20. Patterson Re, Kristal A, Tinker L, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. Ann Epidemiol 1999; 9(3): 178-87.
21. Pietrobelli A, Formica C, Wang Z, and Heymsfield S. Dual-energy X-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Physiol. 1996; 271: E941-951
22. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. JCO 1993; 39: 939-50.
23. Azjen I. The theory of planned behavior. Organ Behav Hum Decis Processes. 1991; 50: 179-211.
24. Courneya, K.S., Karvinen, K.H., & Vallance, J.K.H. (in press). Exercise motivation and behavior change. In M. Feuerstein (Ed.), Handbook of Cancer Survivorship (pp. xxx-xxx). New York, NY: Springer.
25. Cadmus L, Irwin ML, Alvarez-Reeves M, et al. RCT of exercise on quality of life in breast cancer survivors. Psychooncology. 2009; 18(4): 343-52.

26. Mayne ST, Cartmel B, Scarmo S, Lin H, Leffell DJ, Welch E, Ermakov I, Bhosale P, Bernstein PS, Gellermann W. Noninvasive assessment of dermal carotenoids as a biomarker of fruit and vegetable intake. Am J Clin Nutr. 2010; 92(4):794-800.