LEANer Protocol
NCT03314688
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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL

Protocol Title: Lifestyle, Exercise, and Nutrition Study Early after Diagnosis (LEANer)

Principal Investigator: Tara Sanft, MD

Version Date: 10/11/23

(*If applicable*) Clinicaltrials.gov Registration #: NCT03314688

INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type "Not Applicable" underneath.

3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

1. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 10 years

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2. Does this study have a Clinical Trials Agreement (CTA)?
   Yes☐ **No☒**
   a. If so, does it require compliance with ICH GCP (E6)?
   Yes☐ **No☐**

3. Will this study have a billable service? **Yes ☒** **No☐**

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

4. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes ☒** **No ☐**

If Yes, please answer questions a through c and note instructions below.
a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes ☒** **No ☐**
b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes ☐** **No ☒**
c. Will a novel approach using existing equipment be applied? **Yes ☐** **No ☒**

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

SECTION I: RESEARCH PLAN

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

We propose to examine, in 172 women newly diagnosed with Stage I-III breast cancer who are not practicing the dietary and lifestyle guidelines, and who will receive neoadjuvant or adjuvant chemotherapy as part of their treatment, the effect of a 1-year dietary and physical activity guidelines intervention vs. usual care on the breast cancer outcomes described below. Women will be enrolled either before beginning chemotherapy or following the first chemotherapy infusion but prior to the second chemotherapy infusion (Time 0). Follow up visits will occur post chemotherapy (Time 1), at one-year post-diagnosis (Time 2), ,at two years post-diagnosis (Time 3) and at five years post-diagnosis.

Primary Endpoints: Adherence to Breast Cancer Treatments
Aim 1a: Chemotherapy completion rates (dose amount, number of dose reductions and dose delays)
Aim 1b: Adherence to endocrine therapy in women taking tamoxifen or Aromatase Inhibitors (AIs) at 12- and 24-months after enrollment

Secondary Endpoints: Changes in Biomarkers, Body Composition, Quality of life, pathological complete response (pCR).
Aim 2a: Neuronal calcium sensor 1 (NCS1), Insulin and C-reactive protein (CRP) levels
Aim 2b: Body composition (body weight, BMI, body fat, lean body mass and bone mineral density)
Aim 2c: Changes in Quality of Life (QOL) including cognition
Aim 3: Change in the fecal microbiome
Aim 4a: Determine the association between skin carotenoids pre- and post-chemotherapy and the side effects of chemotherapy (e.g. nausea, neuropathy) in the usual care group.
Aim 4b: Examine the difference in the pre- to post-chemotherapy change in skin carotenoid levels between women randomized to intervention vs. usual care.
Aim 5: Determine pCR, defined as no evidence of viable invasive tumor cells at the primary tumor site and axillary lymph nodes in the surgical specimen, in patients receiving neoadjuvant chemotherapy.
Aim 6: Determine the effect of the coronavirus pandemic on diet, physical activity, cancer care and mental health of LEANer participants.

Exploratory Endpoints:

- Examine the difference in the pre- to post-chemotherapy change in blood-based immune markers between women randomized to intervention vs. usual care.
- Examine changes in epigenetic age acceleration (based on epigenetic clocks using >800,000, methylation sites quantitatively across the genome) and p16, both as biomarkers of aging, from baseline to post-chemotherapy in usual care women
- Evaluate the effect of the lifestyle intervention vs. usual care on change in epigenetic age acceleration and p16 from baseline to one-year.
- Determine the effect of the intervention on longer term (5-year) physical activity, diet quality (healthy eating index) and quality of life.
- Determine breast cancer recurrence and second primary breast cancer.

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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.

Current Dietary and Physical Activity Guidelines for Breast Cancer Survivors: For lowering risk of breast cancer recurrence and mortality, the DHHS, ACS, and WCRF/AICR recommend following a) a dietary pattern that is high in vegetables, fruits, and whole grains, avoids sugar-sweetened beverages, limits consumption of processed and red meats, and limits alcohol intake, and b) an exercise regimen which includes 150 min/week of moderate-intensity aerobic exercise (or 75 min/week of vigorous-intensity exercise) plus two strength training sessions/week and decreasing sedentary time.(1-3)

A growing number of studies have evaluated the impact of following the recommended lifestyle behaviors on cancer risk and mortality. Recently, the VITAL study showed that breast cancer risk was reduced by 60% in women who met the WCRF/AICR recommendations compared with those who did not meet the recommendations.(4) McCullough and colleagues found a 24% lower cancer mortality risk in 6,613 women enrolled in the Cancer Prevention Study-II (CPS-II) who adhered to the lifestyle guidelines (RR=0.76, 95% CI: 0.65-0.89) (5). Despite numerous groups communicating these guidelines, in the CPS-II study, only 4% of women met the lifestyle recommendations. Similarly, in the DIANA trial, at baseline, only 7% of breast cancer patients with metabolic syndrome (and 13% of breast cancer patients without the metabolic syndrome) met the recommendations.(6) While the Iowa Women's Health Study found 34% of the 2,193 female cancer survivors met the recommendations,(7) there is still a large percentage of breast cancer survivors who could benefit from adhering to these recommendations. To our knowledge, no trial has examined, in women newly diagnosed with breast cancer, the effect of practicing the dietary and physical activity guidelines on changes in cancer therapy adherence, biomarkers, body composition or quality of life.

Lifestyle Interventions and Chemotherapy Completion Rate: Few studies have examined how lifestyle behaviors may impact chemotherapy completion rates. A recent publication by van Waart et al evaluated the effect of a home-based, low-intensity physical activity program (Onco-Move) and a supervised, moderate- to high-intensity, combined resistance and aerobic exercise program (OnTrack) compared to usual care on chemotherapy completion rates (i.e., the percentage of patients who would complete chemotherapy without dose adjustments assessed via medical records)(8) The planned chemotherapy regimens and schedules of the three groups were similar and included combinations of anthracyclines, taxanes, alkylating agents, and antimetabolites. In total, 61 of 230 patients (27%) required chemotherapy dose adjustments, with a smaller percentage of OnTrack participants requiring chemotherapy dose adjustments (12%) than those in the Onco-Move (34%) or usual care group (34%), p = .002. The average dose reduction among those who required chemotherapy adjustment in OnTrack and Onco-Move was 10%, compared with 25% in usual care; P=.014, with neuropathy being the main reason for dose adjustments.

This study was the first to replicate the previously observed positive effect of exercise on chemotherapy completion rates in Courneya and colleagues' exercise intervention trial in 242 breast cancer survivors initiating adjuvant chemotherapy.(9) Women were randomly assigned to usual care (n = 82), supervised resistance exercise (n = 82), or supervised aerobic exercise (n = 78) for the duration of their chemotherapy (median, 17 weeks; 95% CI, 9 to 24 weeks). While the primary endpoint was quality of life, a secondary endpoint was chemotherapy completion rate. Adjusted mixed-models analyses indicated that resistance exercise was superior to usual care for improving chemotherapy completion rate (p=.033). Relative dose-intensity was 84% in the usual care group compared with 90% in the resistance-training group (P=.033) and 87% in the aerobic exercise group (P = .266). The percentage of

participants who received at least 85% of their planned dose-intensity was 66% in the usual care group compared with 78% in the resistance training group (P = .082) and 74% in the aerobic exercise group (P =.241). Given the exploratory nature of these findings, they should be replicated before the findings are considered reliable. Neither trial included a diet component in their intervention, thus the combined role of following the dietary and physical activity guidelines on chemotherapy completion rates is unknown.

Adherence to Endocrine Therapy: Approximately 70% of all breast cancers are hormone receptor-positive and are amenable to treatment with adjuvant endocrine therapy (tamoxifen or AIs).(7) Current breast cancer guidelines recommend premenopausal women diagnosed with hormone receptor-positive breast cancer take tamoxifen for 5 years, and recommend postmenopausal women diagnosed with hormone receptor-positive stage I-III breast cancer take an aromatase inhibitor (AI) for 5 years or switch to an AI after two to five years of tamoxifen.(10) However, side effects of tamoxifen and AIs have resulted in poor adherence and discontinuation of the drugs. (10, 11) Factors associated with non-adherence to endocrine therapy include low recurrence risk perception, age, medication cost, low socio-economic status, suboptimal patient-physician communication, higher comorbidity, cigarette smoking, lack of social support and lower quality of life. (11-13) Primarily as a result of side effects, up to 50% of patients do not adhere to endocrine therapy as prescribed, and 20% discontinue therapy within the first years of use.(11, 12) Both non-adherence and early discontinuation of AIs have been shown to be independent predictors of mortality. (14)

Specifically, Dr. Dawn Hershman (consultant) and colleagues evaluated endocrine therapy adherence in 8,769 breast cancer patients and found 31% of patients discontinued therapy within 6 months of initiation and of those who continued, 28% were non-adherent (defined as <80% days with prescription supplies per total days of follow-up). (14) Ten-year survival was 81% in women who took endocrine therapy for 5 years vs. 74% in those who discontinued the endocrine therapy early (p <.001), and 82% in women who were adherent vs. 74% for those who were non-adherent (p <.001). After adjusting for clinical and demographic variables, both early discontinuation (HR 1.26 [95% CI 1.09-1.46]) and non-adherence among those who continued to take the medication (HR 1.49 [95% CI 1.23-1.81]) were independent predictors of mortality. Similar findings linking poor AI adherence to an increased risk of breast cancer mortality have also been observed in other cohort studies. (15)

To our knowledge, there have only been three randomized trials designed to test the impact of an intervention on adherence to endocrine therapy, and all three focused on providing educational material describing the benefits of these therapies. (16-18) Findings from these studies demonstrate that educational materials alone do not significantly improve AI adherence. In our recently completed trial, the Hormones and Physical Exercise (HOPE) Study, we randomized 121 breast cancer survivors (of 1016 women screened, 12%) who had been taking AIs for at least 6 months and were experiencing AI-induced arthralgia to a yearlong exercise intervention (with 70% adherence to the twice-weekly strength training and average 159 min/week of aerobic exercise completed) or usual care and found a significant 29% decrease in AI-induced arthralgia in the exercise group compared to a 3% increase in the usual care group (p = .0001). (19) Furthermore, there were no adverse events associated with the exercise program. The HOPE Study was not designed to evaluate the impact of exercise on improving AI adherence, as women were not enrolled prior to initiation of AIs. Hence, questions remain regarding how to improve AI adherence, especially in the first year of taking AIs at time when women frequently discontinue the medication.

Lifestyle Interventions and Pathologic Outcomes: Neoadjuvant therapy is the standard approach for large, locally advanced tumors where surgical resection would be difficult, allowing for tumor shrinkage

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and increasing rates of breast conserving surgery (BCS) (68) Additionally, chemotherapy given prior to surgery allows for in vivo assessment of chemotherapy sensitivity. Patients who achieve a pathologic Complete Response (pCR), in which the tumor has been eradicated by chemotherapy prior to surgery such that there are no remaining viable invasive tumor cells at the primary tumor site and axillary lymph nodes in the surgical specimen, are known to have superior breast cancer-related and overall survival outcomes. (20) (21) Pathologic complete response rates have been used by the FDA to approve drugs; yet, there is a paucity of data regarding how lifestyle interventions affect this important outcome. Some studies have demonstrated that overweight/obese patients have a significantly lower pCR rate compared to patients who are normal/underweight (OR 0.67, 95% CI 0.45-0.99.), while other studies have found that overweight/obese women have lower pCR rates in ER+/HER2+ cancers but higher pCR rates in ER-/HER2+ cancers. (22) Our study will allow us to investigate pCR rates in those who receive a healthy diet and physical activity intervention compared to those who do not. Further, we will control for meaningful covariates including initial BMI, chemotherapy regimen and completion rates, and tumor receptor status. There is a recognized need to evaluate the functional, endocrinologic, and immunologic end points associated with lifestyle modifications and the effects of these on response to therapy. (23)

Lifestyle Interventions and Cancer Biomarkers in Breast Cancer Survivors: We recently completed the Lifestyle, Exercise and Nutrition (LEAN) 6-month randomized trial of healthy eating and exercise in 100 women (of 825 screened, 12%) who had completed treatment for breast cancer. (24) The 11-session intervention (conducted in person or via telephone) was adapted from the 2010 U.S. Dietary Guidelines, ACS and AICR guidelines1-3 and modeled on the diabetes prevention program. We found statistically significant decreases in body weight among women randomized to intervention (-6% mean weight loss) compared to usual care (-2.0% mean weight loss) ($p = .0024$), and a 30% decrease in CRP ($p= .05$) and 10% decrease in insulin ($p= 0.08$) compared with no changes in usual care. Favorable dietary changes were observed as well (see Goals of Intervention section for results on page 10).

Changes in CRP and insulin are clinically important, as previous publications including our own, have shown higher levels of CRP and insulin to be associated with higher risk of breast cancer mortality.56-58 Specifically, in the HEAL study, a prospective cohort study of 710 women with breast cancer conducted by Dr. Irwin and colleagues, higher levels of CRP independently predicted an increased risk of death in women with early-stage breast cancer (p for trend =0.002), even after adjustment for tumor stage, age and body mass index.(25) The investigators also observed a trend toward an increase in breast cancer recurrence in women with higher levels of CRP (p for trend =0.07). The HEAL study also demonstrated an increased risk of breast cancer recurrence in women with higher levels of insulin two years after diagnosis.58 These associations of high CRP, elevated insulin levels and breast cancer mortality have also been observed in other studies. (26)

Evidence suggests that a novel binding protein neuronal calcium sensor 1 (NCS1) is related to neuropathy in patients receiving taxanes, with a suggestive association with cognitive function (27, 28)

Little is known about changes in NCS1 associated with chemotherapy or interindividual variation in change.

While the influence of physical activity and obesity on the immune system in healthy adults has been studied, (29)the impact on the immune system of patients with cancer has not been adequately investigated.

Epigenetic age calculated via DNA methylation is accurate and robustly associated with chronological age across various human tissues and cells.(30, 31) Positive epigenetic age acceleration (EAA) indicates accelerated epigenetic age, suggesting an individual's DNA methylation-predicted age

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is older than their chronological age.(30) To date, EAA has been associated with inflammation,(32) cancer,(33) and mortality.(34) An better understanding of EAA will enable patient stratification for cancer related toxicities and serve as a biomarker for future intervention studies. Few studies have evaluated if longitudinal lifestyle interventions can change EAA(35)·(36) and to our knowledge, there are no data specific to cancer patients. Of note, chemotherapy and radiation have been shown to increase the risk of age-related health issues.(37, 38) Animal data indicate cancer therapies induce cellular senescence.(39, 40) There is intriguing new research on epigenetic age in relation to cancer treatments, including one study in early stage breast cancer patients,(41) suggesting accelerated biological aging after exposure to cancer therapies.(41, 42)

Among the many biomarkers for aging, p16 (also known as $p16^{INK4a}$ or cyclin-dependent kinase inhibitor 2A, CDKN2A) has the advantage that it can be measured in peripheral blood cells (43). Activation and increased expression of p16 is a hallmark of cell aging (44). In contrast, deletion or hypermethylation of p16 promotes cancer by altering cell cycle progression. Both human subjects and rodent models show decreased p16 in cancer cells and elevated expression in aging (45). Stimuli such as physical exercise promote p16 expression and lead to maintenance of dentate gyrus stem cells by maintaining self-renewal capacity of these cells during aging. As the dentate gyrus is critical for spatial and contextual memory formation, maintaining p16 levels is important for preservation of cognitive functions during aging.

Data suggest chemotherapy increases p16 in breast cancer patients.(46, 47) In healthy individuals physical inactivity has been associated with higher p16 expression.(43) Of note, chemotherapy and radiation increase the risk of age-related health issues.(37, 38) Animal data indicate cancer therapies induce cellular senescence.(39, 40)

Exercise Trials and Cancer Biomarkers in Breast Cancer Survivors: A few, small randomized trials have evaluated the impact of exercise alone upon insulin and other biomarkers in women who had completed adjuvant treatment for breast cancer.22-25(48-51) Two of these trials were conducted by our group.(50, 51) The first study demonstrated a 28% reduction in fasting insulin levels at the end of the 1-year intervention in 101 inactive, overweight breast cancer survivors participating in a mixed strength and aerobic exercise intervention.24 The other study (YES study) looked at the effect of a 6-month aerobic exercise intervention in 68 sedentary, overweight breast cancer survivors, and demonstrated a 20% reduction in insulin levels in intervention participants relative to controls (p=0.089).(51)

We have also conducted exercise and educational trials within the first year of diagnosis. We conducted the "Increasing or maintaining physical activity during cancer treatment (IMPACT)" study in 50 newly diagnosed breast cancer patients.(52, 53) The mean time from date of diagnosis to randomization was 11.1 $\pm$ 4.5 weeks (or ~5 weeks from surgery). Women were randomized into either a telephone-based exercise group or a usual care group. Women randomized to exercise were given exercise education materials and provided with weekly telephone counseling by an exercise physiologist with the goal of exercising for 150 min/wk. Women randomized to exercise performed 144 $\pm$75 min/week of moderate-intensity exercise, with 64% meeting or exceeding the 150 min/week goal. Women randomized to exercise also increased their daily walking by 3,555 steps/day (~2 miles per day) from baseline to 6-months compared to 578 steps/day (~0.25 miles/day) in women randomized to usual care (p = .02). Women randomized to exercise also experienced a -0.4 $\pm$ 3.7 kg decrease in body weight compared with a 0.5 $\pm$ 2.9 kg increase in body weight in usual care. Insulin levels decreased in exercisers by 14.5% compared with increases of 20.7% in usual care women (p = .18).

Drs. Irwin and Ligibel also recently completed a pre-surgical exercise trial in women newly diagnosed with breast cancer entitled "the Pre-operative Health and Body (PreHAB) Study (PI: Dr.

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Ligibel, Co-I: Dr. Irwin), which evaluated the impact of an exercise intervention upon breast tumor tissue biomarkers (clinicaltrials.gov NCT01516190). The study enrolled 49 women prior to definitive breast surgery and randomized them to a supervised strength-training and aerobic exercise intervention or to a mind-body control group. Tumor tissue was obtained from the diagnostic biopsy and from breast surgery, and is currently being analyzed for novel biomarkers. Dr. Sanft (PI) and colleagues also conducted a study (DETAILS) of survivorship care plan (SCP) delivery by identifying and enrolling women at diagnosis (which was defined as the post-operative visit to discuss final pathologic staging) to be tracked and given a SCP after treatment completion. She found 100% of eligible women agreed to participate.(54) Our experience with the PreHAB, IMPACT and DETAILS studies in recruiting women within a month of diagnosis into trials strengthens the feasibility and safety of the proposed study.

Body Composition: Obesity at diagnosis has been associated with breast cancer recurrence and breast cancer- and all cause-mortality. (55, 56) Furthermore, we recently published a meta-analysis in JNCI of weight gain after breast cancer diagnosis and associations with breast cancer–specific, all-cause mortality and recurrence outcomes. 31 Twelve studies (n = 23,832) were included in the meta-analysis. Weight gain (≥5.0%) compared with maintenance (<5.0%) was associated with increased all-cause mortality (HR=1.12, 95% CI = 1.03 to 1.22, P = .01). A higher risk of mortality was apparent for weight gain ≥10.0% (HR=1.23, 95% CI=1.09 to 1.39, P<.001).

Weight gain following diagnosis is common. In a recent study that prospectively investigated changes in body weight from diagnosis (before chemotherapy) to 9-months after diagnosis in 272 women, 52% had gained weight, with a mean weight gain of 3.2 kg or 4.97%. At 15-months post-diagnosis, 60% had gained weight, with a mean weight gain of 3.9 kg or 5.9%. (57) Numerous observational studies in women diagnosed with breast cancer have shown premenopausal status and chemotherapy to be risk factors for post-diagnosis weight gain. (58)Chemotherapy-associated weight gain may occur because of reduced physical activity and/or a reduction of resting metabolic rate due to the loss of LBM with a concomitant increase in adipose tissue. (58) Chemotherapy can induce premature menopause in premenopausal women, and women generally gain weight during menopause. A lower BMI at diagnosis (BMI < 25) has also been associated with more weight gain compared with women with a higher BMI. (59)

An additional concern is that weight gain tends to be accompanied by adverse changes in body composition; specifically, gains in fat mass, particularly central adiposity, accompanied by no change or a decline in lean (muscle) body mass (LBM), otherwise referred to as sarcopenic obesity, which in turn results in reduced muscular strength and mobility. (60) Low LBM in patients with cancer has been associated with increased toxicity to anticancer therapy and higher occurrences of metabolic syndrome-related comorbid conditions, with both mechanisms potentially leading to reduced rates of survival. (61) Recent data suggest that lean muscle mass (LBM) may exert a powerful endocrine, immune and hormonal influence within the body, which may affect survival. (62)

Quality of life: Health-related quality of life (HRQoL) is most adversely affected in cancer patients during the time between diagnosis and completion of therapy. Studies have found participation in a 12-month weight loss study in breast cancer survivors was associated with improvement in several quality of life subscale measures including physical, functional, fatigue and anemia subscales. (63)

Skin carotenoids: Many chemotherapeutic drugs, including those used for breast cancer, induce the production of free radicals. Anthracyclines generate the highest levels of free radicals and taxanes generate smaller, but still significant quantities (64). The extent of the role of free radicals on the therapeutic effectiveness of chemotherapeutic drugs is thought to be variable and remains controversial (64). However, free radicals are accepted as responsible for many side effects of chemotherapy that can impact a patient's ability to complete chemotherapy as scheduled (8)(65). Antioxidants quench free

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radicals, and so in theory, have the potential to mitigate chemotherapy induced side effects. Antioxidant supplements are not part of standard practice, and supplement use is generally discouraged by oncologists, due to the possibility that they may interfere with therapeutic effectiveness. Furthermore, large chemoprevention trials have found adverse effects of antioxidant supplements on cancer risk (9, 10). Despite this, a review of studies that examined various antioxidant supplementation during chemotherapy concluded "that antioxidant supplementation during chemotherapy holds potential for reducing dose-limiting toxicities"(65). While dietary supplements often contain high doses of individual micronutrients, food components of the diet can provide lower and natural sources of antioxidants.

Carotenoids are red, orange, and yellow plant pigments that are responsible for the deep colors of many fruits and vegetables. Following ingestion, carotenoids accumulate in human blood and tissues and have long been measured by chemical analysis as the best available biomarker of fruit and vegetable intake. However, there are other health behaviors that cause oxidative stress that also correlate with carotenoid status. It is widely recognized that smoking is associated with substantial reductions in blood carotenoid concentrations (66-68) and obesity is also associated with lower blood carotenoid levels (14); both behaviors are known to cause oxidative stress. Thus, blood and tissue carotenoid levels represent intake, absorption, and metabolism of antioxidants; the latter related to level of oxidative stress. Until recently blood carotenoids were the preferred biomarker for assessing carotenoid status (69).

Little is known about the effect of chemotherapy on carotenoid status; however, chemotherapy has been associated with a reduction of other antioxidants and overall antioxidant capacity in serum (70, 71). In a group of 85 colorectal cancer patients, those who received chemotherapy had a significant decline in antioxidant capacity compared to those who did not receive chemotherapy(71). Similarly, levels of several serum antioxidants declined in 36 patients following cisplatin therapy despite no reported change in dietary antioxidant intake (70).

Since March 2020, the coronavirus pandemic has affected every aspect of life and has impacted patients receiving cancer care in multiple ways, including diet and physical activity, which are the basis of the LEANer intervention.

Summary and Significance: Currently the DHHS, ACS and WCRF/AICR provide diet and exercise guidelines for cancer survivors. Many women with breast cancer do not follow these guidelines, and elect to delay concerted efforts toward following them until active treatment is complete. However, adoption of these recommended lifestyle behaviors soon after diagnosis may prevent adverse changes in body composition and breast cancer biomarkers and may even improve the efficacy of treatment resulting in improved breast cancer prognosis. Further, by increasing our understanding of the mechanisms mediating the association between lifestyle behaviors and breast cancer survival, we will improve our knowledge of how changes in diet and physical activity influence breast cancer outcomes. Lastly, guidelines for breast cancer survivors also overlap with those for diabetes and CVD prevention, the latter being a common cause of breast cancer mortality.

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3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place

a) Experimental Design: The proposed study is a randomized trial evaluating the impact of a dietary and physical activity guidelines intervention vs. usual care on adherence to breast cancer treatments, body composition, and changes in biomarkers in 172 women newly diagnosed with breast cancer who will receive neoadjuvant or adjuvant chemotherapy as part of their treatment The intervention will be conducted in person in the breast clinic at Smilow Cancer Hospital/Smilow Care Center and/or via telephone/video over one-year. When possible, assessments (4 in total) will be completed at a study baseline clinic visit (after diagnosis for women receiving neoadjuvant chemotherapy and after breast surgery for women receiving adjuvant chemotherapy, but prior to the second chemotherapy infusion) and post chemotherapy, at 1- and 2-yrs post-diagnosis. If not possible for a patient to travel to New Haven for the in-person study assessments, the patient will complete online or/and hard copy study questionnaires. These may be administered by phone. The assessments conducted at the in-person visit are optional at all timepoints. The assessments include: physical exam (height, weight, waist and hip circumference), DXA scan, blood and urine collection, grip strength and carotenoid assessment. Following publication of the initial primary results the manuscript will be mailed to all study participants. Participants who consented to be recontacted will be asked if they are willing to participate in a 5-year follow. Five-year follow up will include assessment of dietary intake, physical activity, and quality of life, similar to these 1- and 2-year assessments. Data regarding breast cancer recurrence, mortality and medical usage will be abstracted from the EMR.

Table 1. Eligibility Criteria

Inclusion Criteria:

- Diagnosed with Stage I-III breast cancer
- Adjuvant or neoadjuvant chemotherapy is part of breast cancer treatment
- Physically able to walk
- Able to complete forms and understand instructions in English
- Agrees to be randomly assigned to either intervention or usual care group

Exclusion Criteria:

- Women who have already i received their second chemotherapy infusion
- Women already practicing dietary guidelines
- Women already practicing physical activity guidelines
- Are pregnant or intending to become pregnant in the next year
- Recent (past year) stroke/myocardial infarction or congestive heart failure
- Presence of dementia or major psychiatric disease
- Women who are malnourished (PG-SGA assessment)
- Participating in a meal replacement weight loss program

Study Population: We will enroll 172 women over 2.5 years (~ 8-9 women/month). Women will be enrolled prior to their the second neoadjuvant or adjuvant chemotherapy session. Given treatments are often of a longer duration for stage IV (which includes recurrent breast cancer) breast cancer, women with stage IV will not be eligible. Patients with recurrent cancer, independent of whether they have received chemotherapy at the time of initial diagnosis, or the time that has elapsed since the initial diagnosis, are eligible. The treatment of the recurrent cancer must be intended to be curative.

In addition, since a healthy diet and physical activity, independent of BMI, significantly contribute to breast cancer mortality risk reduction,(72, 73) we chose to limit inclusion criteria to women not practicing the diet and physical activity guidelines, but not to restrict on BMI (Table 1).

b) Recruitment: Women newly diagnosed with breast cancer will be recruited from a) the Smilow Breast Clinic at Yale-Smilow Cancer Hospital and the Smilow Care Centers b) Columbia University c) Dana Farber Cancer Institute (DFCI) Several recruitment strategies will be used.

1. Yale-Smilow Cancer Hospital and the Smilow Care Centers:

i) Regular meetings with the breast surgeons and medical oncologists will be held to tell them about the study and assess for eligible patients attending the clinic. Prior to the patient starting chemotherapy, the surgeon or medical oncologist or their staff will provide each eligible breast cancer patient a study brochure and ask if the research team may contact them to discuss the study. The information regarding the patient's permission for the study team member to contact them will be relayed to the study team either (i) verbally to a study team member if the study team member is in the clinic with the physician OR (ii) via an email from the physician or a member of her/his clinical team. Shortly thereafter, a member of the research team will conduct a screening visit, either meeting with the patient in-person or calling the patient. Women who meet the eligibility criteria and are interested in the study will be consented either in-person or verbally (via the telephone) with use of the information sheet, depending upon feasibility of travel. If willing, the patient is scheduled for an in-person baseline visit which will be conducted at the Hospital Research Unit located on the 10th Floor of the East Pavilion of YNHH. (52-54)

ii) The clinic schedules of medical oncologists at the Smilow Breast Center and the Smilow Care Centers will be reviewed on a regular basis to identify newly diagnosed breast cancer patients and determine potential eligibility for LEANer (i.e. those breast cancer patients who meet the study eligibility criteria based on a targeted EPIC review). During the mandated time of working remotely, screening forms will be completed, scanned using the Turboscan phone app. and the resultant PDF document emailed between staff. An email will be sent to the patient's medical oncologist requesting consent to contact potentially eligible patients. Physicians are not contacted regarding patients who have opted out of research – JDAT provides access to a list of patients who have opted out of research in EPIC. If the physician gives consent (either verbally or by email) to contact the patient, one of the study team will call the patient to describe the study, assess interest in the study and complete the screening eligibility assessment. Physician consent to contact the patient will be documented in the patient's research chart if obtained by phone. If consent is obtained by email, the email correspondence will be stored in the dedicated Yale study email. Women who meet the eligibility criteria and are interested in the study will be consented either in-person or verbally (via telephone) with use of the information sheet, depending upon feasibility of travel. If willing, the patient is scheduled for an in-person baseline visit which will be conducted at the Hospital Research Unit located on the 10th Floor of the East Pavilion of YNHH.

Data on all patients identified will be maintained to ensure patients are not recontacted for participation during the 5-year study, and so inferences can be made regarding characteristics of study participants at the end of the study.

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2.Columbia University

A recruitment flyer will be posted and made available to patients at the Breast Cancer Program of the Herbert Irving Comprehensive Cancer Center at Columbia University; the leader of the Breast Cancer Program, Dr. Dawn Hershman, is a consultant on the LEANer study. Interested patients will be asked to contact Yale study personnel, who will describe the study in detail and screen for eligibility. Screening will include collection of data on cancer stage (Stage IV patients are ineligible) and treatment (patients are ineligible if they are not prescribed chemotherapy) in addition to the standard screening data (e.g. minutes per week of exercise). Patients who consent to the study will be asked to sign a medical record release form to allow collection of data on breast cancer diagnosis and treatment, including prescribed chemotherapy regimen and completion of chemotherapy (e.g. dose reductions, delays, and reasons for dose reductions and delays). Patients relevant medical records will be requested at the end of chemotherapy. Women who agree to enroll in the study will be required to provide information on number of chemotherapy sessions planned, hormone receptor and HER2 status as this information is required for study randomization.

3. Dana Farber Cancer Institute (DFCI Study Site)

Dr. Jennifer Ligibel (PI at DFCI) and her staff will identify, screen, recruit, and consent interested and eligible patients. For patients who consent to participate in the study, the patient's name, address and contact information (phone numbers and email address) and disease related information (e.g. stage, hormone receptor and HER2 status, chemotherapy regimen, treatment plan) and screening form will be provided to the Yale study team to enable study randomization. PHI will be transferred by fax or a method of secure file transfer. Women will complete the self-administered questionnaires either online or hard copies will be provided. The Yale team will inform the patient if randomized to usual care or intervention. If the patient is randomized to the intervention arm the Yale dieticians will conduct the intervention as per study protocol, including mailing the intervention material to the patient. Study questionnaires at the post chemotherapy, year-1 and year-2 visits will be completed online or hard copy. No in-person assessments will be conducted. Staff at DFCI will collect chemotherapy completion data following each chemotherapy session.

c) Study Assessments:

Women will be asked to complete the self-administered study questionnaires prior to the in-person baseline visit. They will be provided a link via email to the online questionnaires or given a hard copy version if preferred.

Assessments	Screening	Baseline	Post-chemo	1-year	2-year	5-year
Screening Questionnaire	X					
Demographic Questionnaire*		X				
Medical History Questionnaire*		X				
Food Frequency Questionnaire		X	X	X	X	X

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Phone assessment 24-hour dietary recall – 1-day[&1]		X	X	X	X	
Physical Activity Questionnaire		X	X	X	X	X
Patient Global Assessment (SGPGA)	X					
PROMIS quality of life questionnaires(74)		X	X	X	X	X
Prescription Medication		X	X	X	X	X
Adherence to medication questionnaire(75, 76)				X	X	X
Neuropathy – EORTLC QLQ-CIPN20(77)		X	X	X	X	X
Work history			X	X	X	X
Beliefs about Medication Questionnaire(78)				X	X	X
Treatment Satisfaction Questionnaire for Medication(79)				X	X	X
Health Insurance, prescription coverage and prescription refill habits				X	X	X
Medication usage questionnaire				X	X	X
Aromatase Inhibitor/Tamoxifen usage form				X	X	X
Breast Cancer Prevention Trial (BCPT) Symptom Scales (80)		X	X	X	X	X
Brief Pain Index		X	X	X	X	X
Homunculus		X	X	X	X	X
Y5-Lymphedema Questionnarie						X
Supplement intake/over the counter medication *		X	X	X	X	X
Y1 -Lymphedema Questionnaire				X		
Y2- Lymphedema Questionnaire					X	
Satisfaction Questionnaire (Intervention group)				X		
Side-effects and toxicity assessment (PRO-CTCAE™)		X	X			
Chemotherapy delay/dose reduction/reasons (extracted from EPIC EMR)			X			
Grip Strength[%]		X	X	X	X	
EPIC 2YR follow up treatment form					X	

EPIC 5 Year medical usage and breast cancer status abstraction						X
Two Year Follow up Treatment form'					X	
Height and weight measured%		X	X	X	X	
Waist and hip circumference measured%		X	X	X	X	
Blood collection%		X	X	X	X	
DXA scan%		X	X	X	X	
Urine collection%@				X	X	
Urine collection for pregnancy test if applicable prior to DEXA%		X	X	X	X	
Stool collection%		X	X	X		
Skin carotenoids%		X	X	X	X	

*: Part of the Baseline Questionnaire
%: Applicable only to the Yale site when in-person visits are completed. Assessments are optional.
@ Applicable to women who are prescribed an aromatase inhibitor
&: Assessment is optional.
1: Discontinued in August 2020.

Note: As of mid-March 2020, in-person visits and associated in-person assessments (DXA, blood and urine collection, weight/height and waist hip measurements, skin carotenoids, stool collection, grip strength) could no longer be conducted due to the coronavirus pandemic. In-person visits and assessment will re-start when allowed by the institution.

Screening Questionnaire: Eligibility criteria will be determined from electronic medical records via EPIC and/or via interview-administered questionnaire during the screening visit.

Screening will include determining eligibility on diet and physical activity by asking the following questions:

1. 'Prior to your diagnosis of breast cancer, did you exercise, *(for example, jogging, walking on a treadmill or stationary bicycling)?'

If the patient reports exercising less than 150min/wk moderate aerobic exercise and less than 75 min/wk of vigorous aerobic exercise (e.g. running) or an equivalent combination they are coded 'no' on the exercise criteria

2a. 'Prior to your diagnosis of breast cancer, how many servings of vegetables did you usually eat per day (don't include French fries)?'

2b. 'Prior to your diagnosis of breast cancer, how many servings of fruit did you usually eat per day?'

A card describing serving sizes will be provided for the patient's reference.

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Eligibility Criteria for fruit and vegetable intake: < 7 fruit and vegetables combined per day
If the patient reports eating less than 7 fruits and vegetables per day, they are coded 'no' on the healthy eating criteria

To be eligible, participants need to respond 'No' to both questions.

These two guidelines have been used as screening criteria in other diet and physical activity trials. (81, 82)

In addition, we will administer the Patient-Generated Subjective Global Assessment (PG-SGA) (83). If malnourished a patient will be ineligible for the study.

All patients who are screened by phone following receipt of MD consent to contact and who are ineligible for the study or do not wish to participate in the LEANer study, will be asked if they would be willing to be contacted about participation in future studies.

Medical history and demographic questionnaires: The following will be assessed via questionnaire prior to enrollment and at 1- 2- and 5-years (when applicable): reproductive and menstrual history, medical history, family history of breast and other specific cancers, and history of tobacco and alcohol. Menopausal status will be defined at diagnosis as 12 months of amenorrhea; perimenopause will be defined as amenorrhea for 3 months in the previous 12 months. Self-report of menses is viewed as reliable to define menopausal status, especially since serum hormonal levels are highly unreliable in the perimenopausal transition phase. To confirm therapy and other treatments, the following will be abstracted from medical records via EPIC: surgery, presence or number of involved axillary lymph nodes, hormone receptor status, disease stage, tumor size, chemotherapy therapy and evidence of completion (see also our section on chemotherapy completion rate); type of endocrine therapy (if applicable) including start date (see section on Adherence to Endocrine Therapy). All current prescription and over-the-counter medications will also be inventoried.

Physical Activity: Women will complete a physical activity questionnaire to assess current (past week) and past year (i.e., year before diagnosis) physical activity levels. Hours/week spent in different types and intensities of activity (including sedentary time) will be computed over the past week and year before diagnosis, as well as at 1-year 2-year and 5-year follow ups.. This physical activity questionnaire has been used in all of Dr. Irwin's previous studies and has been extensively published and shown to be valid and reliable.(19) Women randomized to intervention will be given Fitbit devices which will be used as an objective measurement of physical activity. Participants will wear the Fitbits and they will be encouraged to wear the Fitbit at all times and record the steps per day in their LEANer log.

Dietary Intake: Women will complete 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 (discontinued August 2020).(84) FFQs will be administered at baseline, post-chemotherapy, 1- and 2-years. The FFQ will be completed at the 5-year follow up. Subjects will have the option of completing an online version of the questionnaire. A link will be sent to the subject

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to allow completion. No PHI will be collected by the Fred Hutchinson Cancer Research Center who oversee collection of the FFQ data. No IP addresses are accessed/collected.

Adherence will be assessed via attendance to counseling sessions, as well as by adherence to the diet and physical activity recommendations (assessed via questionnaire at baseline, 1, and 2 years). Women randomized to intervention will also complete a daily log book where they log their daily food, beverages and physical activity (similar to our LEAN and HOPE studies). At each counseling session, the dietitian will review the log book either in person or via phone reporting.

*Weight and Height: Weight and height will be measured by research staff at baseline, post chemotherapy, 1- and 2-years. Participants will be weighed in light 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. (Yale in-person visit only)

*Waist and Hip circumference: Waist and hip circumference will be measured at baseline, post-chemotherapy, 1- and 2- years. Each measurement will be taken twice by a research member. (Yale in-person visit only)

*Grip strength will be measured by a simple to administer modified sphygmomanometer (Detecto DHS Series, Northbrook, Illinois). The participant will be asked to squeeze the balloon of the sphygmomanometer three times with maximal force. The average value of three trials for each hand will be recorded. Higher scores (reported in kPa) reflect better grip strength. (Yale in-person visit only)

Pain: Pain will be assessed using the Brief Pain Index (85). Arthralgia will be assessed using a self-assessment tool where patients are asked to mark 'yes' were asked to mark painful joints on a homunculus with circles showing upper and lower extremity joints, and four areas of the back and neck, and additional diagrams of both hands (three joints on each finger and thumb) and both feet (joints at the base of each toe). (76).

Body Image: Body image will be assessed using the PROMIS assessment.

Supplement intake/over the counter medication: These will be assessed using a questionnaire used in prior studies overseen by Dr. Irwin.

Prescription medication: Patients will be asked to self-report current prescription medication usage.

*Dual Energy X-Ray Absorptiometry (DEXA) scans: DEXA scans will be used to assess body fat percentage, LBM and bone mineral density at baseline, post-chemotherapy, 1- and 2-years. The DEXA measurements will be made with a Hologic scanner (Hologic 4500 with a "Discovery" upgrade, Hologic Inc, Waltham, Mass). All DEXA scans will be evaluated by a radiologist who will be blinded to the intervention group of the participant, and a quality control phantom will be used daily for calibration. Women of childbearing potential will be required to complete a pregnancy test prior to the DEXA scan. Women who are pregnant or intend to get pregnant during the 2-year study time period are excluded from the study. Women who can get pregnant will have a pregnancy test prior to each DEXA scan, if the pregnancy test is positive the woman will not be able to enroll in the study or, if already enrolled, will no

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longer be able to participate in the study. However, the data collected prior to pregnancy will be included in the study. (Yale in-person visit only)

Quality of Life (QOL): Women will complete the PROMIS questionnaire to assess physical, emotional, social, and functional well-being as well as fatigue and overall quality of life (74) ,at baseline, post-chemotherapy, 1- 2- and 5-years. (86) They will also complete the EORTLC QLQ- CIPN20 to assess peripheral neuropathy (77), the Breast Cancer Prevention Trial Symptoms Checklist

Work History: Women will complete a questionnaire on work history which can be impacted by chemotherapy (87).

Medical Usage: At the Year 5 timepoint, the following data will be abstracted from the EPIC EMR: breast cancer recurrence, second primary breast cancer, weight, health care utilization.

*Skin carotenoid assessment: Reflectance Spectrometry (RS) is a quick novel noninvasive method of assessing skin carotenoids(88). Skin carotenoids measures will be conducted at the baseline, post-chemotherapy, 1-year and 2 year visits. The patient will apply gentle pressure on their thumb against the RS lens for less than one minute. Each patient's thumb will be scanned three times. RS values will be recorded on the laptop connected to the instrument. The RS methodology uses a broadband white light to measure skin carotenoids and other chromophores like melanin and hemoglobin directly through their respective absorptions. The reflected light is directed to a spectrograph coupled with a room-temperature detector array. The data processing algorithm corrects for the potentially confounding effects of melanin and tissue scattering (88). (Yale in-person visit only)

Side-effects and toxicity assessment: Women will complete the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) at the BL and post-chemotherapy visits (https://healthcaredelivery.cancer.gov/pro-ctcae/terms_of_use.html).

Lymphedema: Women will be screened for lymphedema the 1-year 2-year and 5-year follow ups by asking the following question 'Since your cancer treatment, have you had any swelling on the same side as your treatment that has not gone away?' If the response is 'Yes' then she will be asked about diagnosis of lymphedema and will complete the Norman Lymphedema Questionnaire. If lymphedema is reported any woman randomized to intervention, she will be instructed to wear a compression sleeve on the affected arm while strength training, and the upper body strength training will follow the model developed by Schmitz et al, in order to avoid lymphedema exacerbations. (89) These exercise protocols have been used by us before and are consistent with recommendations from the American College of Sports Medicine for cancer survivors.(89)

*Biomarkers: Fasting blood (> 12 hours) will be collected at baseline, at completion of chemotherapy and at the 1- and 2-year clinic visit. (Yale in-person visit only) Two 10-ml red-top tubes will be collected for serum, and two 10-ml lavender-top tubes will be collected for EDTA plasma. Technicians will centrifuge the EDTA samples at 2,000 rpm for 15 minutes at 4°C within 1 hour of collection. Plasma and buffy coat will be separated and, along with the serum, will be transferred into cryovials and labeled with freezer-proof labels with participant ID #s and date. All specimens will be stored temporarily at 4°C after aliquotting prior to delivery to our freezer (within 2 days), and then stored at -80

degrees C until analysis. Each woman's baseline and follow-up samples will be assayed in the same batch, and an equal number of intervention and control samples also will be included in each batch. Appropriate blinded quality control samples (low and high levels) will be used to monitor the reliability of each assay.

Insulin will be measured in serum using an enzyme-linked immunosorbent assay (ELISA) kit (DSL-10-1600, Diagnostic Systems Laboratories, Inc., Webster, TX). *CRP* will be measured with direct chemiluminescent immunoassay on the Immulite analyzer (Diagnostic Products Corporation (DPC, Los Angeles, CA). *NCS1* levels will be analyzed in Dr. Barbara Ehrlich's laboratory at the YSM. In addition, a panel of over 200 proteins potentially related to neuropathy will be analyzed at MD Anderson Cancer Center.

Immune markers

Olink: 92 inflammation, immuno-oncology, and metabolism proteins will be measured in blood plasma samples using Olink Biosciences's multiplex proximity extension assay (PEA). The 96 protein targets include cytokines, chemokines, markers that have been implicated in immunotherapy response (e.g., PD-L1, LAG3), and tumor or immune cell metabolism (e.g., ARG1, FBP1). Protein levels will be expressed as normalized protein expression and $\log_2$ transformed prior to statistical analysis. The protein levels in the intervention group will be compared with standard of care controls.

RNAseq: mRNA will be extracted from buffy coats using the RNeasy Plus Kit (Qiagen) according to the manufacturer's instructions. RNA sequencing will be performed at the Yale Center for Genome Analysis (YCGA). Gene expression differences between intervention and standard of care samples will be determined using "DESeq2" R package.

Genome Wide Methylation for EAA

The MethylationEPIC BeadChip (Illumina; San Diego, CA) will allow us to interrogate >800,000, methylation sites quantitatively across the genome at the Yale Center for Genome Analysis. A sample of pooled female DNA is routinely included on each BeadChip as a control throughout the experiment and assessed for reproducibility using a Pearson R2 coefficient. We will set to missing data points with detection p-values >.001 and will exclude any samples with probe detection call rates < 95% as well as those with an average intensity value of either <50% of the experiment-wide sample mean or < 2000 arbitrary units (AU). To limit confounding due to positional effects, samples for each person will be run in the same row.

P16 Human p16 ELISA Kit (LSBio) will be used according to manufacturer's instructions.

*Stool collection: A stool collection kit, collection and mailing instructions will be provided to each participant to collect a stool sample in their home as baseline, post chemo and 1-year. Stool will be returned by pre-paid Fed Ex delivery to the Yale School of Public Health. Samples will be frozen and then sent for analysis to outside laboratories (Metabolon and Rob Knight at UCSD). Women who are randomized after their first chemotherapy session (but prior to their second session) will not be asked to complete the stool collection at baseline or thereafter as their stool microbiota may have been affected by the chemotherapy so change in microbiota would be uninterpretable.

Analysis of Chemotherapy Completion Rate: Chemotherapy completion rate will be assessed (via medical records in EPIC) as the average relative dose-intensity (RDI) for the originally planned regimen

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based on standard formulas. We will measure the number and percent of patients requiring dose-adjustments, who have dose-delays, the reason for the dose-adjustment/dose delays (e.g. neuropathy or vacation) and the percent dose reduction for each participant and by group, similar to Courneya and van Waart's papers.(8, 9) All relevant data will be extracted from EPIC (electronic medical records).

Analysis of Pathologic Complete Response: Pathology reports will be used to evaluate residual tumor after neoadjuvant chemotherapy. Pathologic complete response will be defined as no evidence of viable invasive tumor cells at the primary tumor site and axillary lymph nodes in the surgical specimen, regardless of the presence of non-invasive breast cancer or DCIS (Tis); i.e., yT0/TisN0.

Adherence to Endocrine Therapy: Currently, there is no gold standard for assessing medication adherence. Adherence can be estimated from prescription and medical claims and pharmacy databases, medical record review, hospital databases, pill counts, patient self-reports, and pharmacologic assessments of drug concentrations. In the proposed study, we chose to measure endocrine therapy adherence via urinary AI levels as an objective measure of AI continuation rates at 1 and 2 years at the beginning of the clinic visit. A single 15-mL urine sample will be collected and tested for the presence of AI using a previously validated assay that was used in Hershman and colleagues study. (90) In addition to in-person collection of the urine sample, women will be offered the option of home collection of an early morning urine sample, which can be shipped overnight in a pre-paid package to Dr. Lingeng Lu at YSPH, 60 College St, New Haven, CT 06510 who will process, freeze and store the urine sample prior to analysis. All collection and shipping materials will be provided to the participant. The sample will be shipped with cool packs to maintain a temperature of less than 4 degrees centigrade. This option has been added as many women are not able to attend in-person visits due to COVID restrictions or a reluctance to attend in-person visits during the COVID pandemic. This option will be offered to women who completed written informed consent or verbal informed consent. An addendum to informed consent will be obtained if the participant is willing to collect at home urine samples. Dr. Hershman and colleagues are assessing endocrine therapy continuation rates via urinary levels in an NCI SWOG trial of text-messaging and endocrine therapy continuation rates (clinicaltrials.gov NCT01516190). They recently published a study that examined the feasibility of using a urine assay as an objective biomarker of endocrine therapy continuation rates. (90) They found that the assays were highly sensitive at detecting low levels of endocrine therapy in the urine. Our trial will use the same methodology as Dr. Hershman's trial and samples will be analyzed at the Yale School of Public Health.

We will also collect patient self-reported adherence data. 4. The following adherence to medication questions will be self-administered at the Year 1 and Year 2 visit.

1."In the past month, how often did you take your medications as the doctor prescribed?" Possible responses are all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (<50%). Nonadherence is defined as 75% of the time or less.

2. "In the past month, how often did you forget to take 1 or more of your prescribed medications?" Possible responses were never, once in the past month, 2 to 3 times in the past month, once per week, several times per week, and nearly every day. Nonadherence is defined as forgetting to take prescribed medications once per week or more.

3. "In the past month, how often did you decide to skip 1 or more of your prescribed medications?" Possible responses were the same as for question 2. Nonadherence is defined as deciding to skip medications once per week or more. The first will be the primary measure of non-adherence. (73,74) (75) If women switch AIs or from AI to tamoxifen, we will capture this, but classify them as having continued endocrine therapy and therefore adherent. All women who discontinue tamoxifen or AI will

be asked to indicate their rationale(s) via an interview-administered questionnaire. Note: The self-reported adherence questionnaire will be completed independent of whether a urine sample is collected.

Beliefs about Medication Questionnaire: Participants will complete the Beliefs about Medication questionnaire at baseline, 1 2 and 5 years. (78) We will also collect additional information about factors potentially influencing adherence at those 3 time points including: out-of-pocket costs, number and type of other prescriptions (from EPIC), degree to which the patient believes in the drug's efficacy, recurrence risk perception, and social support. These factors as well as age, education, smoking, comorbidities, chemotherapy, and any endocrine therapy side effects they experience during the trial will be examined in relation to endocrine therapy adherence.

COVID-19 Questionnaire

In July 2020, all women who are or who have been (if they agreed to future contact as indicated on the study consent form) participants in LEANer will be invited via email to complete an online or hard copy survey regarding the effect of the coronavirus epidemic on their cancer care, and their mental health, diet and physical activity. A link to the survey, which will be hosted on the Qualtrics platform, will be included in the email invitation with instructions on how to get the hard copy questionnaire if desired. The survey will take approximately 10-15 minutes to complete. A study staff member will follow up by email, text message or phone to confirm receipt of the invitation to complete the survey and answer any questions.

Newsletter: A newsletter will be mailed to all participants at 6-monthly intervals while enrolled in the study informing them of the progress of the study and providing relevant information with regard to breast cancer survivorship issues.

All assessments denoted * above are conducted at the in-person visits and are optional.

d) Randomization: Participants will be randomized into one of 2 study arms using a random permuted block design of varying block size in a 1:1 ratio (N=125 to intervention, 125 to usual care). To ensure participants with similar characteristics are equivalently assigned to the 2 groups, we will stratify on the following factors that may be associated with some of the study endpoints:

i) chemotherapy regimen (≤ 4 cycles vs. >4 cycles)
ii) hormone receptor status (ER/PR+ or not)
iii) HER2 status (HER2+ve or not)

Resulting in six strata.:

a) HR/PR+ve, HER2-ve, ≤4 cycles
b) HR/PR+ve, HER2-ve, >4 cycles
c) HR/PR-ve, HER2-ve, ≤4 cycles
d) HR/PR-ve, HER2-ve, >4 cycles
e) HR/PR+ve, HER2+ve, >4 cycles
f) HR/PR-ve, HER2+ve, >4 cycles

The following study personnel will be masked to participant study arm: clinic medical staff performing the DXA scan and laboratory analysis.

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Usual Care Group: Both our usual care group and intervention group will be provided with standardized breast cancer follow up care and materials regarding treatment (i.e., chemotherapy and endocrine therapy when relevant). Current chemotherapy regimens vary from 3 months to 5 months. About one-third of patients will receive four cycles of chemotherapy every 3 weeks, a total duration of ~3 months. About two-thirds of patients will receive four cycles of chemotherapy every 2 weeks followed by 12 weekly cycles of chemotherapy, a total duration of ~ 5 months. Each patient sees her medical oncologist at each chemotherapy session, and also at one- and two-months post-chemotherapy, and then every 3-6 months thereafter up to two years. Patients are seen semi-annually or annually; those on endocrine therapy are monitored by their oncologist semi-annually.
Holiday cards will be mailed to all women while in study.

Lastly, we will also give women randomized to usual care a lifestyle intervention book and log book for breast cancer survivors and access to the associated online videos (approved for HIC protocol 1410014716).. Women will also be offered a counseling session with a registered study dietician at the end of the study.

Dietary and Physical Activity Guidelines Intervention Group:
When and Where: Patients receiving chemotherapy see their medical oncologist at least monthly during chemotherapy and then monthly or bi-monthly, ultimately tapering to semi-annually for several years. Thus, we have designed our intervention to be implemented in the breast clinic when the patient is seeing her medical oncologist. All intervention sessions can be completed by phone or video if this is the preference of the subject. Our LEAN study compared in-person lifestyle counseling to telephone-counseling, and found similar effectiveness on changes in diet and physical activity. For the proposed study, we have adapted our LEAN intervention to include a total of 16 x 30-min sessions over 12 months (3 times in the first month, then 2 times each month for months 2 through 5, and then 5 times over the next 6 months) timed with their oncology visit or via telephone or video (doxy.me) if preferred.

Content of LEAN Counseling Sessions: Our dietary intervention is to counsel women on eating the recommended diet for cancer prevention and control, which focuses on diet quality and nutrient density, which are essential, especially when and if appetite is changed or diminished from treatment. The intervention is based on the LEAN protocol, which was developed by Drs. Irwin, Sanft and Ms. Harrigan. All counseling sessions will be conducted by a registered dietitian. The intervention represents a core curriculum, using motivational counseling to address behavior strategies such as self-monitoring, goal setting, stimulus control, problem solving, and relapse prevention training. The intervention sessions are based on constructs of social-cognitive theory. The nutrition counseling promotes a predominantly plant-based diet, with extensive education on skill building to track portion sizes, fat grams, reduce simple sugars (including sugar sweetened beverages), limit consumption of salty foods and increase dietary fiber intake, resulting in an increased nutrient-dense eating pattern (see Table 3). Maintenance of a healthy BMI is also one of the recommended DHHS, ACS and WCRF/AICR lifestyle guidelines and associated with lower breast cancer mortality. Thus, our LEAN intervention, focusing on portion control and primarily a plant-based diet, will likely lead to better weight management. All topics are accompanied by a homework assignment. Of these, recording daily food intake and physical activity are the most important. Reported portion sizes, grams of fat, added sugars and fiber from the food journal will be compared with individualized goals at each counseling session. Women will also receive our 16-chapter manual adapted from the LEAN manual and a set of adapted recipes. The five new sessions that will be offered

Table 3. Lifestyle Guidelines

Physical Activity Guidelines

1. 150+ min/week of moderate to vigorous intensity physical activity or 75 min/week of vigorous-intensity physical activity
2. Twice-weekly strength training
3. Reduce sedentary time

Dietary Guidelines

4. Eat a combination of 5+ fruits and/or vegetables servings/day
5. Reduce simple sugars
6. Limit consumption of processed and red meats to ≤ 18 ounces/week
7. Limit alcohol consumption to 1drink/day or 8 drinks/week

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will occur latter 6 months with 5 additional monthly sessions. These new topics will focus on issues relevant to women receiving therapy and the nutrition impact of treatment-related side effects. Topics to be discussed are: (1) Anticipating and managing treatment side effects: dysgeusia, nausea, mucositis, diarrhea, xerostomia change in appetite; body image changes, importance of hydration, managing liquid sugars; (2) Managing fatigue, meal timing, meal composition; (3) Managing expectations of others: Food is love, Comfort eating; (4) The importance of nutrition and strength training with endocrine therapy; and (5) Late effects of treatment: cardiac health, lymphedema, fatigue, fear of food, and fear of recurrence. Modifications to food texture, flavor and selection of tolerated nutrient-dense foods will be made on an individual basis to ensure adequate macronutrient and micronutrient food intake, and optimal glucose management.

Physical Activity: The physical activity program, similar to our LEAN and IMPACT studies, will rely on home-based exercise, with an emphasis on brisk walking and reaching a goal of 2.5 hour/week of moderate-intensity exercise and 10,000 steps walked each day. Reducing sedentary behaviors will also be encouraged through activities of daily living. The LEAN program increased physical activity levels by 116 min/week compared to 18 min/week among women randomized to usual care ($p < .01$). (24) For the trial, we have enhanced the physical activity program offered in LEAN, by including a home-based strength training program, developed by Dr. Kathryn Schmitz for breast cancer survivors with lymphedema. (91). Each patient will be given a set of weights (3lbs and up) to use at home as instructed by the study health counselor. A series of study videos will be available online at the study website showing women how to complete each strength training exercise with and without weights, a LEAN Strength Training Program manual will also be provided. Participants will record the type and duration of exercise they do in their log book provided to them. We will also include a tool-box approach, as was done in the Diabetes Prevention Program, where we will provide participants with a 1-year membership to a YMCA close to their home to exercise in poor weather if they so wish, and Fitbits to motivate participants to increase their daily exercise. Participants will also be encouraged to complete the Livestrong program or a similar program at the YMCA

Goals of the Intervention: The goal of the intervention is for participants to adopt and practice the recommended dietary and physical activity guidelines. We will measure adherence to the dietary guidelines by whether participants meet the Healthy Eating Index 2010 (HEI-2010), as it aligns with the DHHS 2010 dietary guidelines, and has been found to be a valid and reliable measure of diet quality. We will update with HEI-2015 when available and we will also evaluate changes in intake of food group, total energy and energy from fat.

Procedures to Enhance Adoption of the Lifestyle Guidelines: Adherence will be assessed via attendance to counseling sessions, as well as by adherence to the diet and physical activity recommendations (assessed via questionnaire at baseline, 1, and 2 years). Women randomized to intervention will also complete a daily log book where they log their daily food, beverages and physical activity. At each counseling session, the dietitian will review the log book. Women randomized to intervention will also be given a Fitbit. The account will be accessible by both the subject and the research team to allow data to be accessed by the research team members. We have also developed an intervention book (adapted from the LEAN book). The books provided to the intervention group include information on skills to support behavior change. Consistent with social cognitive theory, (92) the information will emphasize increasing self-regulatory skills and using cognitive behavioral techniques such as cognitive restructuring, modeling, monitoring behavior, seeking social support, and self-reward. In summary, we designed the intervention based on our trials and to be scalable and implemented in the breast clinic.

To help those women in the intervention group comply with the intervention goals during and following the COVID-19 pandemic, all women who have been assigned to the intervention group will be emailed

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i) the link to the YouTube video in which Dr. Melinda Irwin discusses the conduct of the LEANer study during the pandemic and how to adapt exercise regimens during COVID-19 restrictions. https://www.youtube.com/watch?v=p7mA6tbIQz8.

ii) the link to video on safe grocery shopping practices during pandemic https://youtu.be/3TtHg5XgZzI

The videos will also be provided on the LEANer website tab accessible only by the intervention group participants.

Note: All patients will also be referred to the Yale Cancer Center Survivorship Clinic at the time of the post-chemotherapy visit, where they can if they wish attend up to 2 one-on-one sessions with our registered dietitian, Maura Harrigan, and physical therapist/exercise trainer, Scott Capozza. Holiday cards will be mailed to all women while in the study.

4. Genetic Testing ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned

- Blood-based immune markers analyzed via Olink: 92 inflammation, immuno-oncology, and metabolism proteins will be measured in blood plasma samples using Olink Biosciences's multiplex proximity extension assay (PEA). The 96 protein targets include cytokines, chemokines, markers that have been implicated in immunotherapy response (e.g., PD-L1, LAG3), and tumor or immune cell metabolism (e.g., ARG1, FBP1). Analyses will be conducted at Yale.
  RNAseq: mRNA will be extracted from buffy coats using the RNeasy Plus Kit (Qiagen) according to the manufacturer's instructions. RNA sequencing will be performed at the Yale Center for Genome Analysis (YCGA).

- Epigenetic clocks using >800,000, methylation sites quantitatively across the genome) and p16, both as biomarkers of aging.

ii. the plan for the collection of material or the conditions under which material will be received
Blood samples collected and stored as per study protocol (page 13 and 25) will be utilized for genetic analysis.

iii. the types of information about the donor/individual contributors that will be entered into a database
Data collected as part of the study will be entered into the study databases. No additional data will be collected pertaining to genetic testing.

iv. the methods to uphold confidentiality
The blood samples will be labeled with ID number and timepoint. Identifiable data will not be shared with the teams analyzing the blood samples. Data from the genetic analysis will be stored on password protected computers or on a shared drive with restricted access.

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B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
Data exchanged between the researchers and internal organizations serving this project, such as the Yale Center for Genomic Analysis, will carry only the coded identifiers. Any sharing of materials and/or distribution for research projects will be required to have HIC approval and appropriate data sharing agreements will be put in place.

C. Is widespread sharing of materials planned?
No, we do not plan widespread sharing of materials.

D. When and under what conditions will materials be stripped of all identifiers?
Samples will be stripped of all identifiers if a participant withdraws from the study.

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?

How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

Material will be destroyed if not yet anonymized if a participant wishes to withdraw their blood sample.

F. Describe the provisions for protection of participant privacy
Samples will be identified only by ID. Identifiable data will not be shared with the teams analyzing the blood samples. Data from the genetic analysis will be stored on password protected computers or on a shared drive with restricted access.

G. Describe the methods for the security of storage and sharing of materials
Material will be stored in a locked freezer at a Yale secure facility until analysis. Shared materials will be transported by study personnel or an approved courier. Samples will be identified only by ID and collection timepoint.

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

We will enroll a total of 172 women who are planning to undergo chemotherapy at the Smilow Breast Center or a Smilow Care Center, Columbia University or Dana Farber Cancer Institute (DFCI) All women aged over 18 are eligible. Given treatments are often of a longer duration for stage IV breast cancer, women with stage IV will not be eligible. In addition, since a healthy diet and physical activity, independent of BMI, significantly contribute to breast cancer mortality risk reduction, we chose to limit inclusion criteria to women not practicing the diet and physical activity guidelines, but not to restrict on BMI. As material is only available in English, non English speaking women will not be included.

6. **Subject classification:** Check off all classifications of subjects that will be <u>specifically recruited for enrollment</u> 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

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☐Non-English Speaking ☐ Prisoners ☐Economically disadvantaged persons
☐Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses
☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? **Yes** ☐ **No** ☒

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

   Inclusion Criteria:
   - Diagnosed with Stage I-III breast cancer
   - Will receive neoadjuvant or adjuvant chemotherapy as part of breast cancer treatment
   - Physically able to walk
   - Able to complete forms, understand instructions and read intervention book in English
   - Agrees to be randomly assigned to either intervention or usual care group
   - Aged 18 or over

   Exclusion Criteria:
   - Women who have had their second chemotherapy infusion
   - Women already practicing dietary or physical activity guidelines
   - Are pregnant or intending to become pregnant in the next year
   - Recent (past year) stroke/myocardial infarction or congestive heart failure
   - Presence of dementia or major psychiatric disease
   - Women who are malnourished (PG-SGA assessment)
   - Participating in a meal replacement weight loss program
   - Non English speaking

8. How will **eligibility** be determined, and by whom?

   Study eligibility will be determined by study personnel in concert with Drs. Sanft and Irwin.

9. **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 dietary and physical activity guidelines intervention group for the first year of the study. During this time, the counselor will inquire about each participant's overall health and how she is adapting to the dietary and physical activity guidelines intervention 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.

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The blood draw will occur at YCCI (in the Hospital Research Unit of YNHH) 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 0.04 rads (40 mrem) (a total of 0.08 rads (80 mrem) at each visit as both a bone density DEXA scan and body composition DEXA scan will be performed at each of the 4 visits). The total exposure over the 2-year study is 0.32 rads (320 mrem) which is equivalent to a uniform whole body exposure of 390 days (approximately a year) of exposure to 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 risks associated with the stool, urine collection or with the measurement of grip strength. There are no known risks associated with the skin carotenoid scan using reflectance spectroscopy.

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 known 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. Some of the research data will be collected via an online survey hosted by Qualtrics (http://www.qualtrics.com/) during the study visit. Permission has been granted by Yale ITS for use of Qualtrics for the online survey and a Business Associates Agreement has been issued by Yale University. Survey responses will be recorded and stored on Qualtrics' secure website, accessible only to study staff through unique passwords. Note, no PHI will be collected when completing the online FFQ. The IP address is not accessed or collected. Video counselling will use doxy.me, which is HIPAA and HITECH compliant. All data is encrypted, no information is stored from sessions. Doxy.me can be used for patients who do not have MyChart access. Data collected at DFCI will be transferred to Yale by Secure File Transfer or other secure method.

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. Tara Sanft (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.

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

    Effective screening will exclude all subjects who would be at greater risk for complications because of medical or psychiatric illnesses. All efforts will be made to protect subjects' confidentiality. This is described in detail below.

11. **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.)

a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk

b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A

c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for

i. Minimal risk
ii. Greater than minimal
iii.

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

The principal investigator, the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. Adverse events are defined as injury possibly associated with participation in the physical activity component of the intervention. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the principal investigator.

d. For multi-site studies for which the Yale PI serves as the lead investigator: YES.
How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? The protocol represents minimal risks to the subjects and adverse events are not anticipated. Adverse events are defined as injury possibly associated with participation in the physical activity component of the intervention. In the unlikely event that a serious, unanticipated and related adverse event occurs, it will be reported in writing within 48 hours to the Yale HIC, DFCI IRB and within a week to the NIH. Yale study staff will inform DFCI study staff within 48 hours if they become aware of any adverse events occurring in patients enrolled at DFCI.

What provisions are in place for management of interim results? The Principal Investigator will evaluate the adverse events and study data at regular intervals (every quarter) and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent and authorization form are required.

What will the multi-site process be for protocol modifications? The Yale PI will inform the DFCI site of any protocol changes via email.

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Statistical Analyses: Statistical analyses will be conducted by the Yale Center for Analytical Sciences, which provides extensive statistical support to Yale Cancer Center. Analyses will be performed using SAS v9.3. The statistical design is a two-armed, randomized intervention study. The primary objective is to examine the effect of the intervention on relative dose intensity of chemotherapy, adherence to endocrine therapy at 12- and 24-months, with the secondary aim of evaluating the intervention on biomarkers, body composition and quality of life.

Relative dose intensity will be calculated using the methods described by Longo et al [24]. The primary endpoint, RDI will be analyzed both as a continuous scale using the t test, and as a dichotomized outcome using 85% or 95% cut-off for Mantel-Haensel chi-square test controlling for stratification factors. In addition, group differences in chemotherapy completion rates will be analyzed with binary logistic regression analysis; whether or not having dose reduction during the period of chemotherapy treatment (the period between T0 and T1) will be the dichotomized dependent variable. The outcome of endocrine therapy adherence will be assessed at the 2 and 5-year follow ups (as most, if not all, participants prescribed endocrine therapy will have been taking it for at least 1 year at the 2-year visit, allowing us to assess adherence to endocrine therapy). The primary endocrine therapy outcome will be adherence to endocrine therapy assessed via the electronic medical records. Note: the assessment for the primary outcome of endocrine therapy adherence was changed from the initial assessment (urinary metabolites) as the COVID pandemic limited our ability to collect urine samples.

Secondary assessments of endocrine therapy will be:

a) Urinary AI level. An undetectable level will classify the participant as nonadherent to AIs.

b) Responses to the following questions:

(1) “In the past month, how often did you take your medications as the doctor prescribed?” Possible responses are all of the time (100%), nearly all of the time (90%), most of the time (75%), about half the time (50%), or less than half the time (<50%). Nonadherence is defined as 75% of the time or less.

(2) “In the past month, how often did you forget to take 1 or more of your prescribed medications?”

Possible responses were never, once in the past month, 2 to 3 times in the past month, once per week, several times per week, and nearly every day. Nonadherence is defined as forgetting to take prescribed medications once per week or more.

(3) “In the past month, how often did you decide to skip 1 or more of your prescribed medications?”

Possible responses were the same as for question 2. Nonadherence is defined as deciding to skip medications once per week or more. The first will be the primary measure of non-adherence. (73,74).

Participants who report that they have discontinued taking tamoxifen or AI will also be classified as nonadherent to endocrine therapy. For patients who may be lost to follow-up, we will obtain prescription refill data as an endpoint of adherence to endocrine therapy. For the endocrine

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therapy aim, we will compare the crude adherence rates using simple logistic regression. Multivariate logistic regression will serve as supportive analyses including covariate adjustments – which are similar to the primary analysis above.

The secondary aims will be performed using Mixed Model Repeated Measures analysis incorporating Analysis of Covariance, where each woman's changes in outcome (follow-up measure – baseline) will be modeled as a function of treatment and time with a covariate included for the baseline value. Prior to fitting models, we will perform exploratory data analyses focusing on the distributions of biological markers by time and intervention group, assessing the appropriateness of log-transformation.

All hypotheses will be tested 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. Statistical significance will be defined as $p < 0.05$, 2-sided. Since we have multiple outcomes, we will consider using a Bonferroni correction.

Age, menopausal status, race/ethnicity, BMI at diagnosis, disease stage, type of surgery, type of chemotherapy, radiation therapy, hormone receptor status, endocrine therapy, reconstructive surgery, type 2 diabetes, and smoking status will be examined as covariates. We will explore effect modification by menopausal status at diagnosis, hormone receptor status, and endocrine therapy.

We will further explore intervention effects on study endpoints by stratifying by adherence to diet and physical activity guidelines with a four-level category (e.g., met diet recommendations, met physical activity, met both diet and physical activity recommendations, or met neither recommendation). This analysis will allow us to better understand the role of diet vs. exercise on study endpoints.

Although we do not anticipate an appreciable number of subjects lost-to-follow-up because of our plan of following patients during their medical oncology visits, the impact of missing data will be evaluated in the analysis. Bivariate logistic regression will be used to identify baseline variables associated with missingness. The primary analysis assumes missing data are missing at random (MAR). Under the MAR missing data mechanism, the probability of loss-to-follow-up depends only on the observed data. Non-random or informative loss-to-follow-up occurs when the missing data are dependent on the unobserved missing outcome values, latent and/or instrumental variables. Sensitivity analyses using methods for NMAR data will be considered.

Power and Sample Size Considerations: The sample size estimate was performed using PASS 12 (©2013 NCSS, LLC, Kayesvile, UT). The original calculation was based on chemotherapy completion rates reported in the COMPAS study (Ziller etc, BMC Cancer, 2013). By assuming similar completion rate in our control arm, we estimated a sample size of 250 subjects would be needed. Sample size reevaluation was conducted using the aggregated data of first 51 LEANer participants who completed chemotherapy. The pooled standard deviation of RDI is 0.10. We re-estimated that a sample size of 86 subjects per arm (172 total) will achieve 90% power to detect a 0.05 (or 5%) difference in RDI between two arms at significance level of 0.05. For endocrine therapy adherence, the COMPAS study reported 48% of patients in the control group were adhering to AI therapy at 12 months.18 We assume approximately 50% of patients randomized to usual care in our study will be adhering to endocrine therapy at one-year post-initiation of use. Group sample sizes of 76 patients per group (or N = 152) provides 90% power to detect an absolute difference of 25% in the intervention group (50% vs. 75%, adherence in control and intervention groups, respectively) at a two-sided 0.05 significance level. We anticipate ~70% of participants (i.e., 70% of 172 = 120) will be prescribed endocrine therapy; thus an N = 120 will also allow for sufficient statistical power.

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For insulin, our previous studies showed a 25-30% effect size (3.0 µU/mL) and standard deviation of 8.0 µU/mL, which yields a per group sample size of 112 or total N = 224.24 For weight changes, our LEAN study showed a 7% effect size (5.6 kg) and a SD of 4.2 kg in the intervention group compared to 2% (1.7 kg) and SD of 3.7 kg in usual care (P=0.0004). (24) We will have sufficient statistical power to detect smaller effect size since we will have a larger sample size in the current application.

We will not allow participants who are assigned into usual care cross over to intervention group. However, if 10% of 86 participants who are randomized into intervention arm drop out to usual care, we will have 81% power to detect difference of 18% chemotherapy dose adjustment in intervention vs 34% in controls.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. RADIOTRACERS – N/A

B. DRUGS/BIOLOGICS – N/A

B. DEVICES – N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: 133
b. If this is a multi-site study, give the total number of subjects targeted across all sites: 172

2. Indicate recruitment methods below. 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	
☐ YCCI Recruitment database	☒ Clinicaltrials.gov Registry (do not send materials to HIC)	

☒ Other (describe): Regular meetings will be held with the breast surgeons and medical oncologists at Smilow Breast Clinic to tell them about the study and assess for eligible patients attending the clinic. The clinic schedules of medical oncologists at the Smilow Breast Center and the Smilow Care Centers will be reviewed on a regular basis to identify newly diagnosed breast cancer patients and determine potential eligibility for LEANer (i.e. those breast cancer patients who meet the study eligibility criteria based on a targeted EPIC review).

*** Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

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An introductory video will be accessible from the study website for women interested in the study to watch.

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

Potential subjects will be identified either at the Smilow Breast Center or one of the Smilow Care Centers or via review of medical records (EPIC). Either the patient's physician will ask the patient if they wish to be contacted about the study at the in-person clinic visit, or the study team will send an email asking the physician for email or verbal permission to contact a potential subject identified via a review of medical records.

The study will be advertised at Columbia University and patients can self-refer for the study.

Eligible patients will be identified at DFCI which is a study recruitment site.

b. Describe how potential subjects are contacted.

Subjects will either be seen in-person at the Smilow Breast Center or one of the Smilow Care Centers or will be contacted by telephone.

c. Who is recruiting potential subjects?
Potential subjects will be recruited by the study team members.

4. 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. Dr. Sanft, the Principal Investigator, may be the treating medical oncologist for some of the subjects enrolled.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☒ For entire study- We are requesting a waiver of signed HIPAA authorization for subjects who are recruited remotely (see below).
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

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i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: We need to determine certain eligibility criteria including PHI (e.g. tumor type) prior to contacting a woman to participate in the 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:

We are obtaining verbal HIPAA authorization for study participation, from subjects who are participating remotely.

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.

6. **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.

    1. The entire consent form will be reviewed in detail with the subject in a private, one-on-one setting at the first intake appointment. The intake appointment may be a visit separate to the baseline HRU visit or may be combined with the baseline HRU visit. All risks and potential benefits will be described. Any questions the subject may have will be addressed. If the subject wishes, she may take the consent form home and consider it further before signing. Subjects may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the subject has signed the consent, she may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. A copy of the consent will be provided to the participant.

    OR

    2. When a subject is unable to travel to meet with study personnel prior to the second chemotherapy session (enrollment must be prior to this timepoint) the subject will be offered participation in the study without the requirement of in-person visits to the Hospital Research Unit at Yale New Haven Hospital. This may occur when patients for example when patients from Torrington or Lawrence and Memorial

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(New London) care centers, Columbia University or DFCI wish to enroll in the study. Except for DFCI patients, informed consent will not be obtained in-person but verbal agreement to participate will be obtained with use of the information sheet – see the study information sheet. The information sheet will be reviewed in detail with the subject by phone. All risks and potential benefits will be described. Any questions the subject may have will be addressed. If the subject wishes, she can request that a copy of the information sheet be mailed or emailed to her before she decides whether to participate. Subjects may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the subject has verbally consented to participate in the study, she may withdraw from the study at any time. A copy of the information sheet will be provided to the participant. If an enrolled subject decides that she wishes to complete the later in-person study assessments (post-chemo, 1-year or 2-year) they will be asked to complete in-person consent will be obtained using the study consent form.
At DFCI, patients will be identified, screened and consented by DFCI study staff. All risks and potential benefits will be described. Any questions the subject may have will be addressed. If the subject wishes, she may take the consent form home and consider it further before signing. Subjects may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the subject has signed the consent, she may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. A copy of the consent will be provided to the participant. All subsequent contact with DFCI patients regarding the study will be conducted by Yale study staff. No in-person study visits will be conducted.

<u>At home urine collection for analysis of Aromatase Inhibitors</u>
An addendum to informed consent will be obtained if the participant is willing to collect at home urine samples. This option has been added as many women are unable to attend in-person visits due to COVID restrictions or a reluctance to attend in-person visits during the COVID pandemic. This option will be offered to women who completed written informed consent or verbal informed consent.

7. **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.

   During the consenting process, the research assistant will read and review the consent form/information sheet with the prospective participant. The research assistant will then ask the potential participant various questions about the consent form/information sheet and study protocol to ensure the prospective participant sufficiently understands the study and the nature of their consent to participate.

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8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   We do not plan to enroll non-English speaking participants.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of signed consent:**

☒ **Recruitment/Screening only**

☒ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☐ NO ☒**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☒ (at the time of recruitment/screening) NO ☐**

OR

- Does the research pose greater than minimal risk? **YES ☐ NO☐**

- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☐**

☒ Requesting a waiver of consent:

☐ **Recruitment/Screening only**
☒ **Entire Study**

For a waiver of consent, please address the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐ NO☒**
- Why would the research be impracticable to conduct without the waiver?
  Waiver of consent limited to the genomic analysis. Signed study consent was obtained for those in the study with a blood sample (genomic material) prior to genetic analysis which added after all relevant subjects were off study.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? N/A

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

Name, address, telephone number, email address, date of birth, dates of diagnosis, dates of all treatments, treatment procedures and compliance with treatment, cancer history, pathology reports, comorbidities (e.g. diabetes, heart disease, high blood pressure). Medication history and data on

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medications taken throughout the study. Medical history, including stroke and myocardial infarction. Identifiable information will be collected and used to enroll and contact participants. It will only be used for this purpose. Given that this trial involves enrolling patients who are undergoing active treatment at Smilow Cancer Hospital or one of the Smilow Care Centers, all participants will have a medical record as part of their clinical care. The medical records are in an electronic format (EPIC) on a secure YNHH server apart from the paper research records. EPIC will be accessed by study staff to abstract the relevant participant's medical data and scheduled medical appointments.

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

The research data will be collected via questionnaires (including online questionnaires – see below), DEXA scans, from the EMR/medical records and analysis of blood, urine and stool samples. The data will be collected and stored as hard copy documents (some questionnaires) and electronically (questionnaires, treatment data from EMR, dietary collection, results of blood and stool analysis). Data will be entered into OnCore, a YCCI maintained software program, and other data stored on a Yale secure server which is maintained behind a firewall. Chemotherapy completion data, including delays in chemotherapy, dose reductions and reasons for delays and reductions will be entered in REDcap, a database which is supported by YCCI.

Some of the research data will be collected via an online survey hosted by Qualtrics (http://www.qualtrics.com/) during the study visit. Study staff will create the survey instrument using Qualtrics software and all questions will be formatted to allow for participants to skip any items they do not wish to answer. Permission has been granted by Yale ITS for use of Qualtrics for the online survey and a Business Associates Agreement has been issued by Yale University. Survey responses will be recorded and stored on Qualtrics' secure website, accessible only to study staff through unique passwords.

Video counselling will use doxy.me, which is HIPAA and HITECH compliant. All data is encrypted, no information is stored from sessions.

For patients at Yale or DFCI, data will be collected from the patient rec. Data collected by DFCI staff will be transferred to Yale by Secure File Server or an express mail carrier (e.g. FedEx). For patients who self-refer from Columbia University, medical records will be requested to be either faxed to a fax machine located in the study office or to be mailed to the study office.

As a participant in a clinical research study involving the Yale-New Haven Hospital (YNHH) Research Unit (HRU) information from the study HRU visits are added into the medical record. Therefore, a subject's previous medical records of other visits or admissions will be available to the researchers and to the staff of the HRU when entering the visit data.

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

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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 and after the subject's participation in the study?

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

All questionnaires and samples will be identified with the participant ID number and date of collection as the only identifiers. Any information published as a result of the study will be such that it will not permit identification of any participant.

A Data and Safety Monitoring Plan has been established for this protocol. The Principal Investigator will evaluate the adverse events and study data at regular intervals (every quarter) and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent and authorization form are required. During the review process the project Co-Leaders will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the Principal Investigator, the Yale IRB, or the NIH have the authority to stop or suspend the study or require modifications. The protocol represents minimal risks to the subjects and adverse events are not anticipated. Adverse events are defined as injury possibly associated with participation in the physical activity component of the intervention. In the unlikely event that a serious, unanticipated and related adverse event occurs, it will be reported in writing within 48 hours to the Yale IRB, and within a week to the NIH.

e. 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.

The hard copy data will be stored in a locked room and electronic data maintained on secure server for 10 years after the final data is collected. Data will then be deidentified and hard copy data destroyed.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The PI, co-investigators and the research staff, will have access to PHI. Organizations that have a responsibility for protecting human participants, including the Yale Human Investigation Committee and the Yale Cancer Center Office of Protocol Review and Monitoring, may have access to subjects' medical records containing PHI. Additionally, the funding agency (National Cancer Institute) may have access to subjects' medical records containing PHI.

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g. If appropriate, has a Certificate of Confidentiality been obtained? The study is covered by a CoC as it is NIH funded.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported. NO.

SECTION V: POTENTIAL BENEFITS

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 adhering to a healthy lifestyle affects compliance with chemotherapy and hormonal therapy in breast cancer patients. The benefits to the participants in the intervention group may include better knowledge of healthy lifestyle habits (diet and physical activity) during and following chemotherapy and hormonal therapy.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

   The alternative is not to participate in the study.

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

   There will be no payments made to the participants. Parking costs incurred at the time of the baseline, post-chemotherapy, 1-year and 2-year YCCI/HRU visits will be paid by the study. Participants in the intervention arm will be provided with a Fitbit, a set of weights and if requested a 1-year membership at a gym used by the study e.g. YMCA All patients will be given a copy of the American Cancer Society ' New Health Eating Cookbook) at the 2-year timepoint and a cookbook at the 5-year timepoint

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 will be no cost to the subject of participating in the study.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

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b. Will medical treatment be available if research-related injury occurs? Yes

c. Where and from whom may treatment be obtained?

d. Are there any limits to the treatment being provided?

e. Who will pay for this treatment?

f. How will the medical treatment be accessed by subjects?

This is a minimal risk protocol. 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.

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