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

Randomized exercise trial on aromatase inhibitor arthralgia in breast cancer survivors

Irwin, et al

DOI: 10.1200/JCO.2014.57.1547

YALE UNIVERSITY SCHOOL OF MEDICINE
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Research

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

Title of Research Project:
Hormones and Physical Exercise (HOPE) Study

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

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

SECTION II: GENERAL INFORMATION

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

a. Internal Location[s] of the Study:

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

b. External Location[s]:

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

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

☒ *YCCI-Scientific and Safety Committee (YCCI-SSC)	Approval Date: 3/18/09
☐ *Pediatric Protocol Review Committee (PPRC)	Approval Date:
☒ *YCC Protocol Review Committee (YRC-PRC)	Approval Date: 3/12/09
☐ *Dept. of Veterans Affairs, West Haven VA HSS	Approval Date:
☐ *Radioactive Drug Research Committee (RDRC)	Approval Date:
☒ YNHH-Radiation Safety Committee (YNHH-RSC)	Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC)	Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR)	Approval Date:

☐ Dept. of Lab Medicine request for services or specimens form

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

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. July 1, 2009 - June 30, 2013

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

a. targeted for enrollment at Yale for this protocol? N = 180
b. expected to sign the consent form? N = 180
c. expected to complete some or all interventions for this protocol? N = 180

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

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

b. **Study Phase** ☐ **N/A**
☐ Pilot ☐ Phase I ☐ Phase II ☒ Phase III ☐ Phase IV
☐ Other (*Specify)*

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

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

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

If yes, where is it registered?

Clinical Trials.gov registry ☐

Other (*Specify*)

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

Yes ☐ No ☒

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

Yes ☐ No ☐

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

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

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

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

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Melinda L. Irwin	RCT of exercise on AI side effects in breast cancer patients	NCI	☐ Internal ☒ External	☒ Grant-M# CA132931 ☐ Contract#
Melinda L. Irwin	RCT of exercise on AI side effects in breast cancer patients	Breast Cancer Research Foundation	☐ Internal ☒ External	☒ Grant-M# ☐ Contract#

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

	Name	Signature ***	Protocol-Related COI?	Affiliation
Principal Investigator	Melinda L. Irwin		☐ Yes ☒ No	Yale
Role: Co-Investigator	Cary Gross		☐ Yes ☒ No	Yale
Role: Co-Investigator	Herbert Yu		☐ Yes ☒ No	Yale
Role: Co-Investigator	James Dziura		☐ Yes ☒ No	Yale
Role: Project Director	Brenda Cartmel		☐ Yes ☒ No	Yale

Co-Investigator	Tish Knobf		☐ Yes ☒ No	Yale
Research Staff	Elizabeth Ercolano		☐ Yes ☒ No	Yale
Research Staff	Scott Capozza		☐ Yes ☒ No	Yale
Research Staff	Linda Gottlieb		☐ Yes ☒ No	Yale
Student	Hannah Arem		☐ Yes ☒ No	Yale
Research Staff	Maura Harrigan		☐ Yes ☒ No	Yale
Student	Yang Zhou		☐ Yes ☒ No	Yale
Role: Staff	Elizabeth Fraser		☐ Yes ☒ No	Yale
Role: Research Staff	Yanchang Zhang		☐ Yes ☒ No	Yale
Role: Research Staff	Martha Fiellen		☐ Yes ☒ No	Yale
Role: Research Staff	Dan Root		☐ Yes ☒ No	Yale
Role: Research Staff	Mary Playdon		☐ Yes ☒ No	Yale
Role: Student	Erikka Loftfield		☐ Yes ☒ No	Yale
Role: Student	Neel Iyer		☐ Yes ☒ No	Yale
Role: Student	Mia Sorkin		☐ Yes ☒ No	Yale Yale
Role: Student	Adrienne Viola		☐ Yes ☒ No	Yale
Role: Student	Bridget Winterhalter		☐ Yes ☒ No	Yale
Role: Student	Norbert Hootsman		☐ Yes ☒ No	Yale Yale
Role: Student	Meghan Hughes		☐ Yes ☒ No	Yale
Role: Student	Olivia Lynch		☐ Yes ☒ No	Yale
Role: Student	Celeste Wong		☐ Yes ☒ No	Yale

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

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

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

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

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

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

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

_____ _____

Advisor Name (PRINT) and Signature Date

Department Chair's Assurance Statement

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

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

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

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

_____ _____ _____
Chair Name (PRINT) and Signature Date

_____
Department

YNHH Human Subjects Protection Administrator Assurance Statement

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

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

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

_____ _____
YNHH HSPA Name (PRINT) and Signature Date

For HIC Use Only

_____ _____

SECTION V: RESEARCH PLAN

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

Primary Aims: To examine, in 121 postmenopausal women diagnosed with hormone-receptor positive breast cancer who have been taking aromatase inhibitors (AI) for at least 6 months and are experiencing at least mild arthralgia originating during AI treatment, the yearlong effect of exercise vs. attention control (health education) on toxic side effects of AI use including:

1. Severity of arthralgia
2. Endocrine-related quality of life (QOL)
3. Mediators/mechanisms influencing the effect of exercise on arthralgia severity
    a. Lean body mass
    b. Body weight and fat
    c. Cardiorespiratory fitness
    d. Muscular strength
    e. Grip strength
    f. Pain pressure threshold (wrist and knee)
    g. Pro-inflammatory markers (interleukin-6 (IL6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP)
    h. Psychological outcomes (self-efficacy, depression, anxiety, and pain-coping skills)

Primary Hypotheses: Compared to women randomized to attention control (health education), women randomized to exercise will experience from baseline to 6 and 12 months:

1. Less severity of arthralgia
2. An increase in endocrine-related QOL
3. Improvement in mediators/mechanisms influencing the effect of exercise on arthralgia severity
    a. Increased lean body mass
    b. Decreased body weight and fat
    c. Increased cardiorespiratory fitness
    d. Increased muscular strength
    e. Increased grip strength
    f. Increase in pain pressure threshold
    g. Decreased pro-inflammatory markers (IL6, TNF-α, and CRP)
    h. Increased psychological outcomes (self-efficacy, depression, anxiety, and pain-coping skills)

Secondary Aims: To explore, in a subset of these women who are not taking bisphosphonates at baseline (i.e., a conservative estimate of 50% or N = 85), the effect of exercise vs. attention control on:

4. Bone Mineral Density (BMD)

Secondary Hypotheses: Among women not taking bisphosphonates at baseline, women randomized to exercise, compared to women randomized to attention control, will experience from baseline to 12 months:

4. An attenuated decrease, maintenance, or increase in BMD

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.

1. Hormonal Therapy for Breast Cancer

Breast cancer is the most commonly diagnosed cancer among American women (1). Approximately two thirds of all breast cancers diagnosed in US women are hormone receptor positive and as such are amenable to treatment with adjuvant hormonal therapy (1). While tamoxifen has historically been the hormonal treatment of choice, recently aromatase inhibitors (AIs) have emerged as an adjuvant hormonal treatment option in postmenopausal women with hormone receptor-positive breast cancer. Multiple studies have compared the efficacy of tamoxifen and the AI's in regards to disease-free survival, time to recurrence, and overall survival, including the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, Intergroup Exemestane Study (IES), the International Breast Cancer Study Group's BIG 1-98 trial, and the MA-17 trial (2-5). Although these trials utilized the AIs in different ways, as primary hormonal therapy or after 2-5 years of tamoxifen, each demonstrated a statistically significant reduction in breast cancer recurrences and disease-free survival in patients treated with the AIs. Thus, a recent American Society of Clinical Oncology technology panel recommended that AIs be used as adjuvant therapy in postmenopausal women with hormone receptor-positive early breast cancer, either as initial monotherapy or after 2-5 years of tamoxifen therapy (6).

2. Side Effects of AIs

Arthralgia

Symptoms of Athralgia

While AIs are now regarded by many to be the standard of care for adjuvant therapy of hormone receptor positive breast cancer, there remains concern regarding the toxicity of these drugs. Cumulative results indicate that arthralgia, defined as pain or stiffness in the joints that is often migratory and not associated with joint deterioration, is one of the major adverse events associated with AI therapy (7). While not all the arthralgia-related symptoms are necessarily joint-related (and indeed some have been shown to be tenosynovial), we hereafter refer to these symptoms as arthralgia, in keeping with the current terminology used in the literature. Arthralgia has been observed among patients treated with both steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs (2,3), and usually includes bilateral onset with symmetrical pain/soreness in the hands, knees, hips, lower back, shoulders and feet, together with early morning stiffness. AI-associated arthralgia has a typical onset within 2 months of treatment initiation (7). Spontaneous symptom resolution is rare during therapy but common after cessation of AI treatment (7). Patients frequently describe feelings of having aged abruptly and are concerned that these musculoskeletal symptoms may be neuropathy or symptoms of metastatic disease.

Incidence and Prevalence of Arthralgia

Arthralgia is quite prevalent and has been reported in over 25% of women taking AIs (7). Dr. Dawn Hershman and colleagues recently examined the prevalence and severity of arthralgia in a community-based sample of breast cancer patients (8). They asked 200 postmenopausal women receiving AI therapy to complete a self-administered questionnaire that focused on joint pain and stiffness. They found that nearly half (47%) described AI-associated joint pain or stiffness, either originating or worsening during AI treatment. Approximately 24% reported new-

onset arthralgia. Although the majority (67%) of patients described moderate symptoms, nearly one fourth had symptoms rated as severe.

In another recently published study, 56 patients with breast cancer not on clinical trials who were receiving AIs in a clinical practice were interviewed regarding occurrence of worsening or new arthralgia and or bone pain after starting AI therapy (9). Arthralgia was reported in 61% of patients. It was severe in 30%, and resulted in discontinuation of the drug in 20% of patients. Similarly, a chart review of 50 patients who were treated with AIs for early breast cancer found that 22% of women had stopped AI therapy due to side effects (10). Thus, because arthralgia is estimated to be one of the more common adverse events associated with AI use and one of the reasons for AI treatment discontinuation (7), there is considerable interest in its prevention and treatment.

Physiological Changes associated with Arthralgia

While arthralgia is assessed via self-report, a recent *Journal of Clinical Oncology* publication by Morales et al (11), and an editorial from Dr. Dawn (12), present results from a prospective study of 17 women initiating treatment with AIs (n=12) and tamoxifen (n=5), and the effect of these hormone therapies on joint changes. They show that the subjective symptoms of arthralgia and joint stiffness are also associated with physiologic changes to the joint and functional impairments. The patients in this study were assessed with serial MRI, measures of grip strength, and completed symptoms self-assessments. In a 6-month period, the majority of women taking AIs were more likely than those taking tamoxifen to have an increase in tenosynovial changes as seen on MRI, and a decrease in grip strength as measured by a simple to administer modified sphygmomanometer, and increased pain and stiffness as measured by questionnaire. Importantly, the objective, easy to reproduce, and inexpensive hand grip test was well correlated with the tenosynovial changes seen on MRI. After 6 months, AI users had a marked decrease in grip strength (-16.28%) ($p = .0049$). AI users were 2.08 times more likely to have a decrease in grip strength (10 of 12) than tamoxifen users (2 of 5). On MRI follow-up, 11 AI patients had worsening of pre-existing changes or new onset of any pathology of joints or tendons. Significant tenosynovial changes were evident; 3.67 (95% CI: 1.22-21.2) times higher risk of worsening for patients on AI than tamoxifen. Worsening of tenosynovial changes on follow-up was strongly related to a higher decrease in grip strength ($r = -.64$, $p = .0074$). The self-report assessment of arthralgia was also strongly correlated with the MRI-assessed tenosynovial changes. This is the first prospective study investigating the AI-associated arthralgia syndrome by means of a standard rheumatologic evaluation including functional assessment and the use of MRI to demonstrate the anatomic substrate. This study showed that after 6 months, AIs induced more pain and functional impairment of the hands and wrists than tamoxifen. While it is not feasible to conduct pre- and post-intervention MRIs in our proposed study (because of the high cost of MRIs and subject burden), we will have participants complete the grip strength test given its strong correlation with MRI-measured tenosynovial changes.

Cause of Arthralgia

Neither the cause, nor the treatment for AI-associated arthralgia is well understood. Investigators have suggested that the majority of symptoms associated with aromatase inhibition are related to the profound estrogen deprivation that arises as a consequence of AI therapy (13). While the exact role of estrogen on pain perception and sensitization is not clear, it is well-known that numerous musculoskeletal complaints increase in prevalence after menopause (14), and hormone replacement therapy has been associated with a decrease in such symptoms (15). Joint pain emanates from nociceptive neurons; normally, these neurons respond to intense pressure and/or painful movements, but in arthralgia they acquire a heightened sensitivity either at the joint itself (peripheral sensitization of the nociceptive primary afferent neurons) or centrally (hyperexcitability of nociceptive neurons in the central nervous system). Central sensitization of spinal-cord neurons amplifies the processing of nociceptive input from the joint, leading to enhanced responses to innocuous stimuli and a perpetuation of the feeling of pain (13). Consequently, mechanical stimuli (such as walking) evoke stronger pain sensations and a heightened pain response than normal. In summary, estrogen has an anti-

nociceptive influence through opioid pain fibers in the central nervous system, and it is possible that the resulting rapid drop in estrogen via AI use may provide a direct pro-nociceptive stimulus for joint pain, and/or remove the protective anti-nociceptive role of estrogen, thereby exposing patients to any underlying joint pathology. The observation that patients treated with AIs often develop bilateral arthralgia implies that changes in central modulation of nociceptive input contribute to symptoms (13).

Another cause of arthralgia may be related to inflammation (16). Specifically, during inflammatory episodes such as those seen in osteoarthritis, a range of pro- and anti-inflammatory mediators, such as IL-6, TNF-α, and CRP, may contribute to pain. These cytokines promote cartilage reabsorption and can cause inflammation. Additional study in this area is warranted to clarify whether those inflammation markers have any association with AI-induced joint pain, and whether exercise decreases arthralgia via decreases in inflammation.

Obesity and Arthralgia

While AI-related arthralgia and subsequent tenosynovial change may be related to estrogen deprivation, and the release of proinflammatory cytokines, additional studies are needed to evaluate other mechanisms behind AI-associated arthralgia. A major risk factor for joint symptoms in breast cancer survivors not reporting them at entry into the ATAC trial was obesity (17). Being obese led to significant absolute increases of 6.2% in joint pain and stiffness. Obese women tend to have higher estrogen concentrations than non-obese women as a result of aromatization from the adipose tissue, so the decrease in estrogen concentration is likely to be greater in this group. Obesity itself is also a risk factor for joint symptoms independent of endocrine treatment. Specifically, obesity is a primary risk factor for osteoarthritis of the knee (18). A recent study showed individuals with a BMI greater than 30 were four times as likely to have knee osteoarthritis as those with a BMI of 25 or less (18). The link between obesity and osteoarthritis may lie in part with inflammation, because obesity and osteoarthritis are both associated with high levels of biomarkers of inflammation, specifically IL-6, TNF-α, and CRP (19). Obesity is regarded as a low-grade inflammatory condition because adipose tissue produces and secretes several proinflammatory cytokines. Thus, it has been hypothesized that obesity's role as a risk factor for osteoarthritis and other chronic conditions, including breast cancer, originates from the elevated production of these biomarkers in obese people. Furthermore, CRP, an acute phase reactant protein whose production IL-6 stimulates in the liver, has been shown to predict osteoarthritis progression over several years. Proinflammatory cytokines alter the development, progression, or both of osteoarthritis through stimulation of reactive oxygen species production and possibly increased osteoclastic bone resorption. It is reasonable to suggest that weight loss will lead to a lowering of inflammatory markers. In previous research, it was found that weight loss (~5% from baseline) using a combination of diet and exercise produced significant reductions in CRP and IL-6 in older obese and overweight adults with knee osteoarthritis over 18 months (20). Our proposed study will examine whether changes in body weight and fat, as well as changes in inflammatory markers, mediate the hypothesized effect of exercise on arthralgia in breast cancer survivors taking AIs. No study has examined this question.

Current Treatment of Arthralgia

While a number of analgesics have been used for arthralgia, none of these has proven entirely satisfactory (21). Current treatments for arthralgia include non-steroidal anti-inflammatory drugs (NSAIDS) and COX-2 inhibitors; however daily use of NSAIDS and COX-2 inhibitors may be contraindicated for long-term use due to potential adverse events on the gastrointestinal tract, heart, and kidneys (7,21). Narcotic analgesics such as tramadol have the drawback of masking rather than curing ongoing destructive processes in the joints. Glucosamine is not of proven efficacy for arthralgia, and topical treatments such as capsaicin and methylsalicylate are temporarily palliative at best. Other therapies such as high-dose vitamin D overlap with treatments to maintain bone mineral density. However, there is no evidence to suggest that bisphosphonate therapy to prevent bone loss also ameliorates symptoms of arthralgia (21). Thus, prompt, ideally nonpharmacologic therapeutic management of arthralgia, such as exercise, is required to ensure continued drug treatment, improved quality

of life and ultimately improved survival. Ideally, symptom relief from AI-related arthralgia should also be through non-pharmacologic mechanisms, such as exercise, so as not to interfere with the therapeutic effect of the drug. Further, many patients do not want to take additional pharmacologic treatments to control adverse effects from cancer treatment, therefore controlled trials of exercise and its efficacy for AI symptoms management is warranted.

Bone Loss

In addition to arthralgia, other adverse effects of AI therapy include bone loss, new-onset osteoporosis and fractures (22). Recently published reports show that women taking AIs experience greater bone loss and/or osteoporosis and fractures compared to women taking tamoxifen or placebo (23). In the BIG 1-98 trial, more patients taking upfront letrozole experienced a fracture compared with those on tamoxifen. Similarly in ATAC, upfront anastrozole was associated with a significantly greater loss of bone mineral density (BMD) than those on tamoxifen at the hip and lumbar spine (23). AI-associated bone loss may be distinct from normal postmenopausal bone loss. Estrogen deprivation that occurs during AI therapy is generally abrupt compared with that occurring postmenopausally. In addition, AI-related bone loss may occur at an accelerated rate (~2.6% bone loss per year with AI-use compared to ~1% bone loss per year after menopause) (24). Low bone mineral density (BMD) is a critical factor associated with pathologic fracture. Decreases in bone density of 10% have been shown to approximately double the risk of fracture, and even modest BMD increases of 2-4% can offer substantial preventative benefit (25). Although medications can be used to alleviate bone loss, such as bisphosphonate therapy, these drugs also cause significant side effects, such as gastrointestinal toxicity, and add to the overall cost of the AI's, which already cost 3-4 times as much as tamoxifen (26). Furthermore, evidence is lacking for the ability of bisphosphonates to ameliorate arthralgia.

Given the association between AIs and bone loss, women taking AIs require lifelong management of their bone health. All patients should undergo BMD screening before starting AI therapy, and should have regular bone health assessments thereafter (23). Dual energy X-ray absorptiometry (DEXA) is a rapid, non-invasive and painless technique that remains the gold standard for measuring and monitoring BMD. In 2003, the American Society of Clinical Oncology published guidelines for the management of bone health in patients with breast cancer, which recommend annual BMD screening (21). Lifestyle advice (e.g., exercise) is recommended in cases of mild-to-moderate bone loss, and bisphosphonate therapy for severe bone loss. While, the use of bisphosphonates for preventing and/or treating AI-induced bone loss has recently been examined in the Z-FAST and ZO-FAST trials (21), no trial has examined the impact of exercise in preventing and/or treating AI-induced bone loss. AI-associated bone loss may be preventable, allowing women to benefit from AI therapy while also being protected against the increased risk of osteoporosis, fracture, and ultimately breast cancer recurrence or death. Nonpharmacologic methods of managing the side effects of the AI's, such as exercise, that may also be associated with improved quality of life, are therefore desired.

Endocrine-related QOL

The low levels of estrogen achieved with AIs also contribute to menopausal symptoms, such as hot flashes, which in turn are associated with a decreased quality of life (27). To date there has been little systematic collection of data, so that the impact that endocrine therapies, specifically the AI's, exert on QOL remains unclear. This is an important area to investigate as the toxicity profile of different ant-estrogens and AIs varies. Dr. David and colleagues recently published an overview of reported adverse events of adjuvant endocrine therapy, focusing on those that are amenable to pharmacologic or nonpharmacologic management without treatment discontinuation (21). They also highlight specific management strategies that may improve QOL and thereby optimize adherence to therapy, which in turn might improve survival. They discuss the finding that across all adjuvant endocrine trials vasomotor symptoms such as hot flashes are the most common side effects (21,27,28).

Recently, an endocrine-subscale was developed and validated (David Cella was a senior investigator on that project) (29). This subscale was designed for use with the FACT-B and comprises 18 items (e.g., hot flashes, night sweats, weight gain). The FACT-B-ES was

used in the Intergroup Exemestane substudy (IES) among 582 patients (27). Prevalence of severe endocrine symptoms at trial entry was high for hot flashes (46%) which persisted among AI users.

3. Exercise and Side Effects of AIs

Exercise and Arthralgia

While the impact of exercise on arthralgia has never been examined in a randomized trial, strength and aerobic exercise have been shown to benefit people with fibromyalgia (30), osteoarthritis and rheumatoid arthritis, significantly decreasing pain while delaying disability and improving function (31). Although studies have generally found that moderate-intensity exercise does not worsen arthritis symptoms, increasing physical activity in this population has been challenging, in part because of the misconceptions about potential harm to joints and concerns with increased pain. Thomas et al (31) conducted a randomized home-based exercise program among 786 men and women with self-reported knee pain. At 24 months, highly significant reductions in knee pain were apparent for the exercise group compared with the control group. Similar improvements were observed at 6, 12, and 18 months. Similarly, Ettinger et al (32) examined the effects of a randomized controlled structured exercise (aerobic and weight-training) program on self-reported pain and disability in 439 older adults with knee osteoarthritis. At 18-months, participants in the exercise group had a 10% lower adjusted mean score on the physical disability questionnaire, a 12% lower score on the knee pain questionnaire, and performed better on the 6-minute walk test (an indirect measure of V02max), mean time to climb and descend stairs, time to lift and carry 10 lbs, and mean time to get in and out of a car than the control group ($p < .001$). These studies suggest that exercise may improve AI-associated arthralgia.

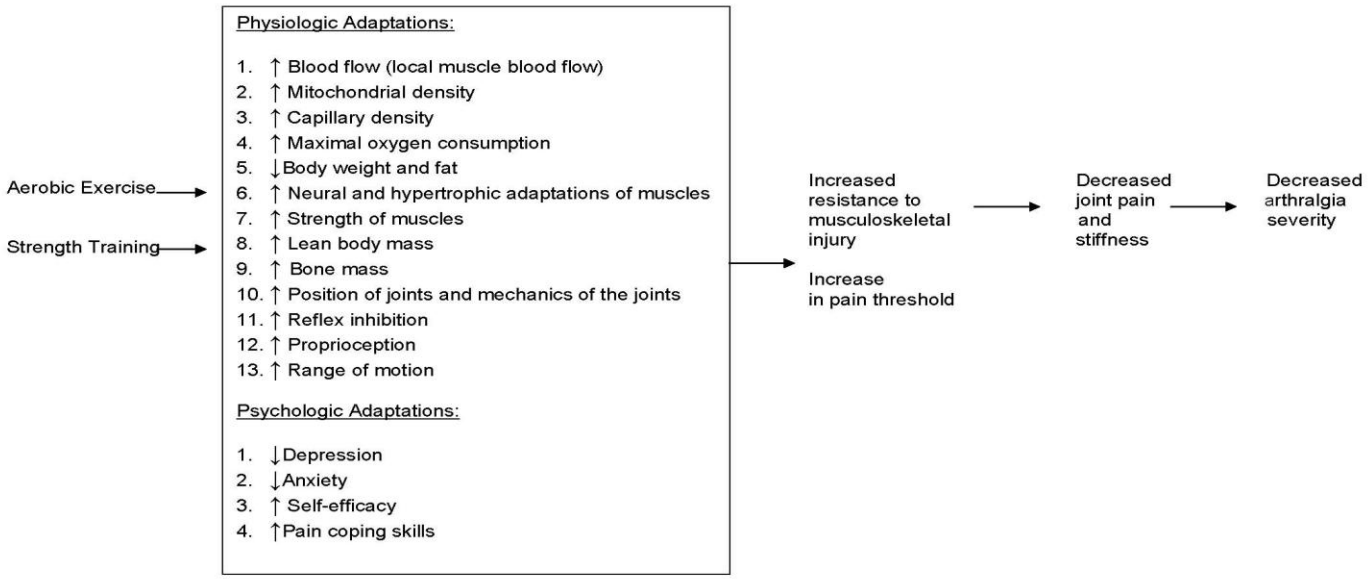
One mechanism by which exercise may improve arthralgia is by improving muscle conditioning and strength. It is hypothesized that one mechanism by which persons with fibromyalgia experience pain is due to muscle deconditioning, leading to muscle microtrauma and therefore pain (33). Further, lack of aerobic exercise has been associated with pain as well (34). Aerobic deconditioning may increase disability, especially in lower extremity tasks such as walking and climbing stairs. Aerobic exercise is associated with improvements in blood flow, including increases in mitochondrial and capillary density, and maximal oxygen consumption, whereas strength training leads to neural and hypertrophic adaptations of trained muscles resulting in increased strength of muscles. Strength training has been shown to effectively improve not only muscle strength in individuals with knee osteoarthritis, but also reflex inhibition, proprioception, disability, and joint range of motion. Exercise may also retard progression of joint damage; joint loading via weight bearing exercise is required to maintain the health and integrity of cartilage (35). Also, in regards to the previous discussion of inflammation and arthralgia, support for a link between inflammation and muscular strength comes from observational data showing that higher IL-6 and TNF-α levels are associated with lower muscle mass and lower muscle strength in elderly persons, and from experimental data in animals showing that administration of IL-6 and TNFα to laboratory animals decreases protein synthesis and increases muscle protein breakdown (36,37). Other physiological factors related to impaired joint function include restricted range of motion.

Other mechanisms include differences in pain threshold for people who exercise regularly, or by other psychological mechanisms (38). Psychological factors such as self-efficacy, depression, anxiety, and pain coping skills have also all been shown to be predictors of pain and disability among individuals with fibromyalgia. Self-efficacy has been shown to be an independent predictor of disability and associated with muscle strength (39), and exercise has been associated with improvements in self-efficacy, depression, and anxiety in breast cancer survivors (40). Regarding pain coping skills, exercise has been shown to activate the sympathetic nervous system (41), and others have demonstrated a link between autonomic regulation (e.g. heart rate) and the endogenous pain modulatory systems (42). Various stimuli to the mechanoreceptors of the joint and periarticular structures (including muscle) due to exercise training might activate descending pain inhibitory pathways and alleviate pain, i.e., the sensory

cortex recognizes the peripheral stimuli as less painful and additional exercise may distract attention from pain (43). Subjectively, resistance training has been associated with decreased pain perception among postmenopausal women with fibromyalgia (44), measured via pain coping questionnaires such as the Coping Strategies Questionnaire. Thus, pain in AI-related arthralgias may be a reflection of sensitization of higher order neurons of nociceptive pathways combined with abnormal endogenous inhibitory systems.

In summary, multiple interrelated physiological and psychological factors influence the pathways linking exercise to improvements in arthralgia severity. If, e.g., mechanical stimuli such as walking is associated with stronger pain sensations, then we hypothesize that an exercise program will improve muscular strength, fitness, lean mass, and bone mass, inflammation, psychological factors, and pain coping skills (via changes in the sympathetic nervous system),which, in turn, will make certain physical activities relatively easier to perform and therefore result in attenuated pain sensations and decreased arthralgia severity (see Figure 1). Some of the factors mediating the effect of exercise on arthralgia have been shown to be related to exercise in healthy men and women, but no study has examined the impact of exercise on arthralgia and its mediators in breast cancer survivors. We hypothesize that exercise will improve arthralgia severity, as well as improve QOL and bone mass. Indeed, few therapies have the ability to be as multifaceted as exercise.

Figure 1. Hypothesized model linking exercise and AI-induced arthralgia in breast cancer survivors.



Exercise and Bone

In non-breast cancer populations, exercise has been demonstrated to improve bone metabolism (45,46). A meta-analysis of 25 randomized exercise trials showed very consistently

that exercise programs prevented or reversed bone loss in postmenopausal women (46). The most studied bone sites were the lumbar spine and hip, where both aerobic exercise (e.g., walking; 1.6% bone loss prevented) and strength training (e.g., 2-4% improvement in BMD and ~5% between group BMD difference (i.e., resistance training vs. control)) had a positive effect. A 5% between-group difference is clinically meaningful given that AI-related bone loss may occur at an accelerated rate (~2.6% bone loss per year with AI-use compared to ~1% bone loss per year after menopause), and decreases in BMD of 10% have been shown to approximately double the risk of fracture; thus, BMD increases of 5% can offer substantial preventative benefit. Thus, exercise training programs should be a strong consideration in the prevention or treatment of bone loss.

While, weight bearing aerobic exercise or resistance exercise has been shown to provide the necessary osteogenic stimuli for bone remodeling, lean body mass (LBM) also plays an important role in maintaining bone mass. Muscle, a component of LBM, exerts a greater force on bones than do other weight-associated gravitational forces, therefore, strongly influencing bone strength and mass. Thus, increasing muscle mass and LBM in this population may provide a protective mechanism against bone loss (47).

While randomized trials have observed a favorable effect of exercise on LBM and/or BMD in healthy postmenopausal women, to our knowledge, only two studies have examined the effect of aerobic exercise and/or resistance training on LBM or BMD in breast cancer survivors who have completed treatment. Dr. Kathryn Schmitz and colleagues investigated a resistance training program on LBM and observed significant increases in LBM (0.88 for exercisers vs. 0.02 for controls, $p < .01$) with a twice-weekly resistance training program in 69 pre- and post-menopausal breast cancer survivors (48). Waltman and colleagues examined, in a 12-month quasi-experimental trial, the impact of a resistance training program on BMD in 21 postmenopausal women with osteopenia or osteoporosis who had completed treatment for breast cancer (49). Over the 12 months, women experienced significant improvements in BMD of the spine and hip ($p < .01$). Results from our pilot study of aerobic exercise vs. usual care on biomarkers of prognosis in 75 postmenopausal breast cancer survivors showed a favorable effect of aerobic exercise (primarily brisk walking) on LBM and BMD ($p < .05$). More importantly though, among the 21 women taking AIs, between group differences for LBM and BMD were 2.8% and 2.0%, respectively, in favor of aerobic exercise compared to usual care. We hypothesize that a combination of aerobic and resistance training would result in even greater between groups differences for LBM and BMD.

In summary, aside from our pilot data, no trial has examined the effect of exercise on BMD specifically in postmenopausal breast cancer survivors taking an AI. Given the strong adverse effects of AIs on bone mass, a trial specifically examining the impact of exercise on maintaining or improving BMD is necessary and of clinical importance. Our trial will provide critical information for women about whether and how much exercise can improve AI-associated BMD loss. Lastly, while bisphosphonates are used by AI-users who are osteopenic or osteoporotic, this medication, similar to AIs, is associated with negative side effects. Therefore, if exercise, a non-pharmacologic approach with no negative side effects, is shown to at least maintain BMD, then exercise may become a routine part of the cancer therapy process especially among women taking AIs.

Exercise and QOL Trials in Breast Cancer Survivors

Numerous studies have examined the relationship between physical activity and well-being, depression, anxiety, physical and emotional functioning, overall quality of life and other psychosocial factors in breast cancer survivors (50). We reviewed all of the exercise and QOL interventions conducted following a breast cancer diagnosis through May 2007. A total of 11 randomized trials have been performed. There were several limitations in these studies, including small samples (N = 10 to 46), short exercise interventions (11 of the 12 studies were less than 12 weeks in duration, and no studies examined endocrine-related QOL including hot flashes. Despite methodologic limitations from these studies, they demonstrate that exercise interventions are feasible in breast cancer patients during and after breast cancer treatment, and they provide preliminary evidence that exercise benefits overall QOL and fatigue in breast

cancer survivors. Among healthy women, several studies have shown that women who exercise regularly have a significantly lower frequency of severe hot flashes (51). Furthermore, available literature suggests that greater body weight is a risk factor for hot flashes, and women who are heavier than ideal body weight may benefit from weight reduction (52). Exercise is associated with weight maintenance (which is especially important among breast cancer survivors who tend to gain weight after a breast cancer diagnosis). The proposed study is novel in that it would be the first trial to specifically address the impact of exercise upon the side effects of the AI's, as well as providing additional data regarding the impact of exercise upon endocrine-related QOL (including hot flashes and weight gain) in women taking an AI for early stage breast cancer.

Exercise and Breast Cancer Survival

Exercise may also be an especially attractive means to manage side effects of AI's, since observational studies have demonstrated a decreased risk of breast cancer risk, recurrence and overall mortality in women who are physically active before and/or after breast cancer diagnosis (53,54). Specifically, our research from the Health, Eating, Activity, and Lifestyle (HEAL) Study, showed women who reported ~2 to 3 hrs/week of moderate-intensity physical activity, such as brisk walking, after a breast cancer diagnosis had a 67% lower risk of death compared to women who were not physically active (55). Our results were similar to the Nurses Health Study findings of lower risk of death with higher levels of physical activity (53). Because of these findings, as well as findings of exercise being related to weight maintenance and improvements in QOL, the American Cancer Society and NCI currently recommend breast cancer survivors participate in moderate-intensity physical activity of 150 min/wk to improve survival. However, it is unknown if this amount of exercise will improve arthralgia severity in breast cancer survivors taking AIs. Our proposed study is highly significant and novel in that it will be the first study to examine the impact of exercise on arthralgia and potential mechanisms, and BMD in a sample of women experiencing joint pain and losses of bone mass. With the identification and treatment of AI-related toxicities (including arthralgia and bone loss) comes the opportunity to prevent or treat these symptoms, with the ultimate goal of improving both adherence to AI therapies, quality of life, and survival.

4. Significance

While the AI's have been demonstrated to improve prognosis in postmenopausal women with early stage breast cancer, their successful implementation depends upon adequate management of their side effects. AI-associated arthralgia has emerged as a major patient concern in adjuvant breast cancer therapy, and clearly warrants rigorous clinical trials to evaluate whether novel treatments may improve symptoms (56). Anecdotal experience, our pilot data, and findings from exercise trials in women with fibromyalgia, rheumatoid arthritis and osteoarthritis suggest that regular exercise may mitigate AI-associated arthralgia. If our trial is successful, it may affect the way postmenopausal women with hormone-receptor positive breast cancer (which comprises ~70% of postmenopausal breast cancer survivors) are treated in the future. Since side effects associated with AI use are quite common, this innovative non-pharmacologic intervention has the potential to benefit a large number of breast cancer survivors, while also being safe and associated with improvements in quality of life and disease-free survival. Lastly, our study will be especially relevant to the mission of NCI and the Office of Cancer Survivorship to improve the quality of life for cancer survivors, support intervention survivorship research, and to ensure best practices for addressing the health needs of survivors. Our study will also extend the NCI Transdisciplinary Research on Energetics and Cancer (TREC) program, which focuses on mechanisms linking physical activity and obesity to cancer, to the cancer survivorship setting.

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

D.1. Design Overview: We propose to examine, in 121 postmenopausal breast cancer survivors who have been taking an AI for at least 2 months and are currently experiencing at least mild arthralgia associated with AI use, the effect of a randomized controlled exercise intervention vs. attention control (health education) on severity of arthralgia, endocrine-related QOL, BMD, and mediators/mechanisms influencing the effect of exercise on arthralgia severity. Women will be randomized to a yearlong exercise program or attention control group. Women randomized to exercise will participate in 150 min/wk of aerobic exercise and a twice-weekly strength training program. We will conduct baseline, six-, and 12-month clinic visits, as well as a 3- and 9-month mailing to evaluate the effect of the intervention on study outcomes.

D.1.a – **6-month intervention study:** A parallel intervention study will be conducted in addition to the 12-month study at Yale only. The study procedures will be the same as those for the 12-month intervention study except where noted in the protocol.

Baseline and six-month clinic visits, as well as a 3- month mailing will be conducted to evaluate the effect of the intervention on the primary study outcomes.

D.2. Resources and Facilities for Performance of Study: The study will be conducted at the Yale School of Medicine. DEXA scans and blood draw (and processing) will occur at the Yale Center for Clinical Investigation. Processed blood will be stored in Dr. Yu's freezer, and he will oversee all inflammatory assays in his lab at Yale School of Medicine. VO2max testing will take place at a facility in New Haven. The exercise intervention will take place at health clubs in close proximity to New Haven, Bridgeport and Greenwich near where patients were treated for breast cancer (see Section D.10).

D.3. Study Population: Women diagnosed with Stage I-IIIC breast cancer will be eligible for the study (see Table 1). AIs are not approved for DCIS, therefore women diagnosed with DCIS are not eligible. Participants must also have been taking an AI for at least 2 months and currently experiencing at least mild arthralgia (defined as = or > 3 on the modified Brief Pain Inventory (BPI) Short Form Questionnaire (67)) that began after initiating AIs.

While the onset of arthralgia *may* occur within the first 2 months of AI initiation, we feel if we include patients too early (i.e., < 6 months since initiating AIs) that the AI-associated side effects and symptoms are most variable during this time period and for some women, the symptoms may lessen on their own. Therefore, we feel it is better to enroll patients with a more stable syndrome (i.e., > 6 months since initiating AIs) given we are prospectively examining the impact of exercise on arthralgia severity. Further, we would like to limit our drop out rate for the study, which may be increased by enrolling patients too early.

To observe a maximal effect from the exercise intervention, only women reporting less than 90 min/wk of moderate-to-vigorous intensity aerobic exercise and no more than one strength training session per week in the previous year, and low fitness level (< 30 ml/kg/min), will be eligible. Because a majority of the US population including breast cancer survivors are physically inactive, we anticipate excluding < 25% of the population based on this criteria (59,60).

Table D.1: Study Inclusion and Exclusion Criteria

Inclusion Criteria:

- Postmenopausal women (defined as the surgical or natural absence of menstrual cycles for at least 1 year prior to breast cancer diagnosis).
- 75 yrs old or younger
- AJCC Stages I-IIIC Breast Cancer
- Taking an AI for at least 2 months
- Currently experiencing at least mild arthralgia (= or > 3 on the BPI) associated with AI use
- Physically able to exercise and physician consent to start an exercise program

- Sedentary activity pattern (< 90 mins/week of moderate-to-vigorous intensity sports activity) within the past year and low fitness level
- No more than one strength training session per week within the past year
- Agrees to be randomly assigned to either exercise or attention control
- Gives informed consent to participate in all study activities
- Able to come for baseline, 6-, and 12-month clinic visits and strength training sessions (Note: only 6-month visit for the 6-monht intervention study)
- Mentally competent

Exclusion Criteria:

- Lymphedema with self reported 'flare up' in the past 4 months

D.4. Recruitment: Recruitment will occur at Yale University and will take 3 years to complete. To identify potential participants, we will use strategies focused on tumor registries and community oncologists, in addition to advertising in the community and on the internet. The tumor registry strategy involves the use of the Rapid Case Ascertainment (RCA) Shared Resource Service of the Yale Cancer Center. The RCA provides the PI with potential participants' names and their physician's names within two weeks of diagnosis. Physicians consent to contact their patients will be passive, that is the physician will be sent a list of women identified as potentially eligible for the study. If a physician has information about a specific patient regarding their participation in the study he/she will be asked to contact the office with this information. If we have had no response from the physician within 2 weeks of mailing the letter, we will mail an invitation letter to the participant, describing the study and telling her that a member of the study staff will be contacting her within a week to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, we will contact her treating physician (likely her oncologist) by mail asking for his/her permission to allow his/her patient to exercise. If we receive permission we will schedule a baseline visit.

The community-oncology strategy involves presenting oncologists with a short synopsis of the study so that when permission is requested to contact the patient, the oncologist is already familiar with the study. Specifically, we will present or provide oncologists with our 10 min powerpoint presentation, as well as our study brochure, describing the study goals, recruitment, data collection, and endpoints. Our goal is to recruit 121 breast cancer survivors over 2-3 years. We anticipate being able to recruit women diagnosed within the past 5 years (i.e., the time period when AIs became widely used). If ~ 2,720 breast cancer survivors are diagnosed per year in CT, we will be able to approach over 10,000 women for participating in our study to randomize 121 women (1.7%). Prior pilot studies of exercise interventions performed at Yale have yielded response rates of 6-40%.

We will use convenience based recruitment strategies in addition those strategies describe above. We plan to post flyers in doctors' offices, public places (e.g. libraries), explore using internet sites that target breast cancer survivors and have our phone number available when the study is reported in the media. If a woman self-refers and appears eligible, her doctors will be contacted to obtain permission for the woman to exercise.

While we only need to recruit 121 women, we will not necessarily approach all 10,000+ women diagnosed with breast cancer in Connecticut over the past 5 years. We will request that our rapid case ascertainment shared resource service of the Yale Cancer Center only provide us with the names of women diagnosed/treated at 1 of the 4 larger hospitals in CT, postmenopausal, and hormone receptor positive breast cancer. While, we are focusing on efficacy (i.e., internal validity) of exercise on improving AI-associated side effects rather than effectiveness (i.e., generalizability or external validity), we do feel that our results will be generalizable given that we are focusing on postmenopausal women taking AIs and experiencing arthralgia (i.e., a large majority of breast cancer survivors). A strength of the proposed study is our population-based recruitment strategy. Most studies use convenience-based recruitment strategies (flyers, media) and are therefore unable to know the actual size of the target population. We will collect information on the population approached (age, ethnicity, education, BMI, physical activity levels, disease stage), and will be able to make comparisons between the women enrolled and the women approached in regards to certain variables.

However, as mentioned, while we feel our results will be generalizable to breast cancer survivors taking AIs and experiencing at least mild arthralgia, our trial will in fact be an efficacy trial. Therefore it is paramount that we focus on internal validity first by having tight control over study eligibility, assessments, and the intervention. If our results show a favorable effect of exercise on arthralgia severity, then future studies may examine the effectiveness of exercise on arthralgia.

D.4.a: 6-month intervention study: women diagnosed with breast cancer will be identified at Yale only.

D.5. Recruitment of Women from Ethnic Minority Groups: Approximately 6% and 4% of women diagnosed within the Yale University area are African American and Hispanic White, respectively. We propose to recruit a sample for this project that is 20% African-American and 10% Hispanic women. While, this proportion of women from ethnic minority groups surpasses the proportion found in the general population of the study area, we will use the cancer registry to assist us in recruiting minorities, as these resources do contain race/ethnicity data (we will target the minority women early in order to maximize the percent of minority women in the final sample).

D.6. Data Collection: Data collection of study variables will take approximately 3 years. The total study is 4 years; thus allowing for 6 months lead up time (manual of operations, set-up, recruit, contact physicians, etc). and 6 months post-intervention for analyses and manuscript submissions. Data collection will involve a screening phone call, baseline interview, baseline clinic visit, 6- and 12-month clinic visit, 3- and 9-month mailing, and a 12-month exercise intervention.

Baseline Data Collection Visits: Baseline data collection will involve a screening phone call, a baseline visit, and clinic visit.

Screening Phone Call: Research staff will call potential participants within one week after they have received a study brochure and an invitation letter. If the participant is interested in the study, the research staff will determine eligibility. If the participant is eligible and interested, a baseline visit will be scheduled for the following week.

Baseline Visit: Participants will be scheduled for a baseline visit at the research staff office or in their home. At the visit, research staff will explain the study in detail and then answer any questions the participant may have. The participant will then sign the informed consent form. The research staff will then interview-administer the questionnaires. The research staff will instruct the participant on a 7-Day Physical Activity Log and Pedometer Log to complete during the following week.

Baseline Clinic Visit: After completion of the baseline visit, the participant will be scheduled (ideally within one week) for a baseline clinic visit. Participants will have anthropometric measurements taken (including height and weight), systolic and diastolic blood pressure, and resting 1-minute pulse. A DEXA scan, to measure total Bone Mass Density, Lean Body Mass, and body fat, will then be taken. Women who are at risk for lymphedema (i.e.have had a sentinal node biopsy or axillary node dissection) will have their arm volumes measured using a Perometer. Research staff will review the physical activity and pedometer logs to confirm that the participant is eligible. Participants will also complete a maximal treadmill test prior to determining study eligibility. A pain pressure threshold test will also be completed. See Section D.10 for more information.

D.7. Randomization: Women 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=75 to intervention, 75 to controls). To ensure women with similar characteristics are equivalently assigned to the 2 groups, we will stratify on factors that may be associated with arthralgia and BMD such as arthralgia prior to diagnosis of breast cancer, prior chemotherapy and BMI ((< 30 kg/m2, > 30 kg/m2) and randomize within each stratum (4 strata in total). It is likely that these variables will be balanced between the 2 groups. We chose to stratify BMI at 30 because of previous studies showing a difference in arthralgia among obese and non-obese women. The following study personnel will be masked to participant study arm: staff performing DEXA scans, study staff reviewing forms and entering data and Co-Is. Only the statistician, study manager, and exercise physiologists will be fully unblinded. After randomization, the exercise participants will be scheduled

immediately for their first exercise and health education session. Attention control (health education) participants will be contacted by phone by a health educator and mailed a booklet which includes health information on topics of interest (also see Attention Control below for more information).

D.8. Follow-up Visits

6- and 12-Month Clinic Visit: The same data that was collected at the baseline clinic visit will be collected in a similar manner at the 6- and 12-month clinic visit. The visit will be ~ 2 hrs. Every effort will be made to have subjects comply. Incentives, such as gift certificates, will be given after completing the 12-month clinic visit.

3- and 9-Month Mailing: We will send questionnaires (e.g. to assess arthralgia,; see measurements below for more information on assessment) to participants at 3- and 9-months.

D.8.a. 6-month intervention study: 6-Month Clinic Visit: The same data that was collected at the baseline clinic visit will be collected in a similar manner at the 6-month clinic visit. The visit will be ~ 2 hrs. Every effort will be made to have subjects comply. Incentives, such as gift certificates, will be given after completing the 6-month clinic visit.

3-Month Mailing: We will send questionnaires (e.g. to assess arthralgia,; see measurements below for more information on assessment) to participants at 3-months.

D.9. Baseline and Follow-up Measurements

Questionnaires Information will be collected on medical history and health habits via a standard questionnaire administered at baseline, 3-, 6--, 9- and 12-months. Specific health habits related to calcium and vitamin D intake and supplementation, chronic corticosteroid use, and alcohol consumption will be included. A screening questionnaire assessing eligibility criteria and any co morbidities will also be administered during a screening phone call.

Physical Activity: We plan to assess physical activity through use of a valid and reliable physical activity questionnaire (to assess different types of activity), completion of a 7-day Physical Activity Log (7-day PAL) (as our primary measure of compliance and adherence to sports/recreational activity) and Pedometer Log. While the 7-day PAL will be our measure of study compliance, our primary analytic plan will be intent-to-treat in that results will be compared between women randomized to exercise vs. control regardless of study compliance. Refer to Section D.14 Statistical Analysis for more detail.

1) a)Physical Activity Questionnaire (PAQ): Study participants will be interviewed, by research staff blinded to the participant's randomization group, regarding their current (past six months) physical activity level using a valid and reliable PAQ (68). This PAQ was used in the YES and IMPACT studies. For each activity done, participants will be asked how often and for how long they performed the activity. Hours/week spent in different types and intensities of activity will be computed over the past six months. The PAQ will be completed at baseline, 6- and12-months in both groups.

b) Exercise Training Questionnaire: Study participants will complete this questionnaire at baseline. Evaluates their anticipated consequences of exercising.

2) Seven Day Physical Activity Log (7-Day PAL): The 7-day DAL will be completed by all participants at baseline (before randomization) and 6- and 12-months as a measure of compliance with the study. We will determine hours per week spent in moderate-to vigorous-intensity sports/recreational activities, and compare values at all time points between exercisers and usual care. We also will use data from the DALs as the primary measure of adherence to exercise among women randomized to the exercise group. Exercisers will complete the log daily and turn it in weekly to the exercise trainer for months 1-12 of the trial. The DAL has been shown to measure daily exercise reliably and validly, when compared with physiological measures of compliance to exercise programs, e.g., VO_2 peak (69), and was also used in the YES and IMPACT studies. When completing the log, women will indicate the sports/recreational activities they performed daily. They also will record the duration of each activity and corresponding heart rate. We will calculate their total minutes per week of moderate- to

vigorous-intensity sports/recreational exercise, and then average the weekly minutes over certain time points, i.e., baseline to 6 months and baseline to 12 months.

3) Pedometer: All women will wear a pedometer and complete the pedometer log at baseline and 12 months. The Yamax pedometer will be used to motivate women randomized to exercise to increase their walking. We chose to use pedometers because they are a low cost motivational aid for increasing physical activity. However, it is important to note that our primary measure of adherence to exercise will be based upon the 7-Day Physical Activity Log, rather than the pedometer. Women randomized to exercise will wear the pedometer for 7 consecutive days every 4 months (i.e., week 1 (one week after randomization), 13, 26, 39, 52). The Yamax pedometer has been tested for validity and reliability and has scored high (r = 0.92 between pedometer steps/day and VO2max) against other objective and subjective measures of physical activity (70). Pedometers were also used in the YES and IMPACT studies. Participants will be given a form to record the number of steps walked/day. When she wakes in the morning, she will attach the pedometer to her belt or waistband and wear it for the entire day (except when bathing or sleeping). When she goes to bed at night, she will take the pedometer off and record steps walked. The data on steps walked per day will be used primarily to motivate women to maintain or increase their steps per day above baseline levels.

Muscle strength testing (exercise group only) will take place at the local health club on the same equipment used for the intervention sessions. Strength changes will be used as measure of compliance to the strength training protocol for the exercise group. Testing will occur at baseline (week 1 of intervention and months 3, 6, 9 and 12). The maximum amount of weight that can be lifted once (1 Repetition Maximum = 1 RM) will be assessed for the bench press and the leg press. One RM tests are the standard by which increases in muscular strength are evaluated (71) and have been found to be safe for most populations when properly supervised (72). After a short treadmill warm-up, and familiarization with the leg press, participants will rate the difficulty (on a scale of 1 to 10, with 10 most difficult) of a warm-up set of 4-6 repetitions (40 lbs. on the leg press). The participant difficulty rating will be used to choose the first weight at which a 1 RM test will be attempted. Resistance will be added until the participant rates the difficulty of lifting the weight once as having a difficulty rating of 10. The same procedure will be repeated for the bench press (starting with 5-lb dumbbells) prior to the end of that measurement visit, with one major exception: participants will be asked to evaluate their symptoms after each lifting attempt and will stop upon symptom change or when the difficulty of lifting the weight once is rated as a 10. At a subsequent visit, at least 48 hours later, participants will again warm-up on a treadmill and resistance will be set at 50% of maximum weight lifted at that prior visit. The participant will be asked to perform 4 repetitions. Then the weight will be set at the highest weight lifted at the prior visit. The participant will be asked to lift the weight once and to continue to perform single repetition lifts (separated by 90 seconds rest) until a maximum weight is reached and recorded as the 1 repetition maximum. This procedure will be followed for the leg press and bench press, again, symptom-limited for the upper body. Trained measurement staff will perform testing at baseline, 3-, 6-, 9, and 12-months and will verbally encourage participants and assist return of the weight stack to the resting position.

Grip Strength Testing: Given the recent strong finding among grip strength, subjective measure of arthralgia, and MRI-measured joint pathology (i.e., tenosynovial changes) in breast cancer patients taking AIs, participants will now complete a grip strength test at baseline, 6-, and 12-months. We hypothesize that grip strength will mediate the effect of exercise on arthralgia. Grip strength will be measured by a simple to administer modified sphygmomanometer (similar to the one used in Morales et al (11). Dr. Irwin already owns this device; 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. All measures will be evaluated by research staff blinded to the intervention group of the participant.

Cardiorespiratory Fitness (VO_2max): Research staff, blinded to the participant's randomization group, will measure each participant's cardiorespiratory fitness at baseline and

12-months with a VO_2 max treadmill test (including 12-lead ECG). We hypothesize that fitness mediates the potential effect of exercise on arthralgia, and therefore we will measure it at these two time points. We will use a modified "Branching Treadmill Protocol". Participants begin at a normal walking speed/0% grade. After 2 min. the speed is increased to a fast walking speed/0% grade. Thereafter, only the grade is increased by 3% every 2 min. Oxygen consumption (VO_2), carbon dioxide production (VCO2), and flow rate will be measured continuously. The test is ended when the participant wants to stop. Resuscitation equipment will be available and staff are trained in cardiopulmonary resuscitation and an Advanced Cardiac Life Support- certified physician is available during all tests.

Arthralgia: In a recent review of arthralgia (7), Burstein recommended some valid instruments to assess arthralgia, such as the Brief Pain Inventory Questionnaire (67), the Western Ontario and McMaster universities (WOMAC) index (73), and the Quick DASH (Disabilities of the Arm, Shoulder and Hand) instrument (74). These measures are also commonly used in the field of rheumatology. Therefore, for the proposed trial, we will specifically ask about upper and lower extremity arthralgia, via these three extensively validated and utilized instruments. Arthralgia will be self-reported at all visits (baseline, 3-, 6-, 9, and 12-months).

In addition arthralgia will be assessed objectively at the wrist and knee by the use of a pressure algometer (Pain Test FXIX25 Algometer) at baseline and 12-month visits. This test will be conducted at the time of the treadmill test. The primary measure of the test is pressure pain threshold. Briefly, the participant will be lying supine with legs extended. The device is placed on the site being assessed (wrist or knee), gradual pressure is applied. The participant is asked to indicate then they first begin to experience slight pain as a result of the pressure.

Screening Question and Brief Pain Inventory: For the proposed trial, in regards to eligibility criteria, women will be asked, "Have you had any joint pain/stiffness in the past week?" and then subsequently asked, "Did this joint pain/stiffness get worse after initiating therapy with an AI?" and "Did you have joint pain/stiffness which started after initiating therapy with an AI?" Furthermore, among those reporting arthralgia, women will complete the modified Brief Pain Inventory Short Form (BPI-SF) worst pain score that asks about their worst pain and/or stiffness in the past 7 days (45). To be eligible for the study, women will have to report a score of 3 or greater (i.e., at least mild arthralgia). These questions were used in Dr. Hershman's studies of arthralgia in breast cancer survivors (8,66).

Specifically, the BPI-SF asks about any joint pain or stiffness in the last week that started after initiating AI therapy, severity of joint paint or stiffness on a 0 to 10 scale, and location of affected joints. This 14-item questionnaire asks patients to rate pain and/or stiffness and the degree to which it interferes with activities on a 0 to 10 scale. Severity is measured as average pain and/or stiffness, pain and/or stiffness right now, worst pain and/or stiffness, and least pain and/or stiffness. The severity composite score will be calculated as the arithmetic mean of the four severity items. Numeric rating scales such as the BPI are among the most common, valid and reliable measures used to assess cancer pain severity, and are preferred by patients over visual analog scale measures (75).

WOMAC: The Western Ontario and McMaster Osteoarthritis Index (WOMAC), first developed over 25 years ago, is perhaps the most widely validated and utilized instrument for evaluating osteoarthritis (OA) of the lower extremity (73,76). Psychometric properties of the WOMAC include: Cronbach's alpha for the pain and disability subscales = 0.81 and 0.91, respectively. The intraclass correlation coefficient for pain = 0.95 and for physical function = 0.92 . Validation studies have shown high correlations with other indices probing the same dimensions (77). The WOMAC instrument evaluates pain (5 items), stiffness (2 items), and physical function (17 items), and takes approximately 5 to 10 minutes to complete. Both the pain scale (5 items) and physical disability scale (17 items) can be analyzed separately. The WOMAC pain subscale consists of 5 items that ask about pain during walking, using stairs, lying in bed at night, sitting, and standing. Each question is scored on a 5-point scale, where 0 = none, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = very severe pain. Total pain scores range from 0 to 20, with higher scores reflecting worse pain. The physical disability

subscale contains 17 items that assess the amount of difficulty subjects say they have with stairs, rising from a chair, walking, and other activities of daily living. Responses are measured and scored in the same way as the pain subscale. The maximum score for the disability subscale is 68, with higher scores reflecting greater disability.

In a study by Thomas et al. (31), participants with self-reported knee pain and knee osteoarthritis were randomized to receive exercise therapy or control. Primary outcome was self reported score for knee pain on the WOMAC index at two years (the WOMAC questionnaire has been the primary outcome measure of self-reported knee and back pain in a number of exercise and arthritis trials). The WOMAC questionnaire has three domains: pain (score 0-20), stiffness (score 0-8), and disability (score 0-68), with higher scores indicating worse outcomes (73). At 24 months, highly significant reductions in knee pain were apparent for the exercise group compared with the control group (between group difference = 0.82, p = 0.001). Similar improvements were observed at 6, 12, and 18 months. Given the WOMAC primarily measures lower body pain, we will also have women complete the DASH Q, which is a valid and reliable questionnaire assessing upper body pain.

Quick DASH (Disabilities of the Arm, Shoulder and Hand) instrument: Upper extremity symptoms will be assessed using the Quick DASH instrument (74). The Quick DASH is an 11-item instrument that addresses both symptoms and physical function of the upper extremities. The Quick DASH represents a subset of the widely used 30-item DASH instrument, which has been used as a primary outcome measure in several prospective studies of women with breast cancer (74,78). The cross-sectional and longitudinal validity of the quick DASH, as well as test-retest reliability, were found to be sufficient to warrant recommendations that either instrument was appropriate to use for longitudinal analyses. Some of the Quick DASH questions include difficulty with everyday activities, work, household chores, recreational and social activities, sleeping, pain severity, and tingling. The point scale is 1 through 100, with 100 representing the most disability. Prior studies have noted that the Quick DASH has a low administrative burden, is quick to score, and is responsive to changes in arm function and symptoms among women with breast cancer. Quick DASH scores have also been shown to reliably identify upper extremity symptoms, as well as patients at increased risk of developing upper extremity disability.

Summary: While the assessment of arthralgia is predominately subjective, and some reductions in this endpoint may occur as an intervention artifact alone, our research design and methods are strengthened by: (1) randomizing women to exercise or attention control. Both groups will receive an equal number of contacts throughout the study from research staff; thus, reducing the likelihood of women responding favorable on the arthralgia questionnaire because of more contact with research staff; (2) only the project manager, exercise trainers, PI and statistician will be unblinded to the participant's group. Thus, study staff collecting and/or managing data will be fully blinded to the participant's group. And lastly, (5) we will conduct a reliability study of the arthralgia questionnaires on at least 10% of the sample.

Dual Energy X-Ray Absorptiometry (DEXA) scans*:* DEXA is the gold standard measure of assessing bone density, osteopenia, osteoporosis, and body fat (79). DEXA scans will be performed at baseline, 6- and 12-months. The DEXA measurements will be made with a Hologic scanner (Hologic 4500 with a "Discovery" upgrade, Hologic Inc, Waltham, Mass). A whole-body scan takes approximately 10 minutes to complete. We will measure percent body fat, Lean Body Mass (kg), bone area (cm^2), and bone mineral density (g/cm^2) overall and of the lumbar spine (L1-L4), and proximal femur (total hip, femoral neck, and greater trochanter). All DEXA scans will be evaluated by a clinical assistant who will be blinded to the intervention group of the participant. Furthermore, a quality control phantom will be used daily for calibration. Hologic Inc also comes out once a year for maintenance and calibration.

Only women not taking bisphosphonates at baseline will be included in the BMD analyses. We conservatively estimate 50% of the sample will be taking bisphosphonates at baseline. Immediately after the baseline visit, prior to randomization, we will be communicating with the participant's oncologist about the exercise program, as well as providing the oncologist with the baseline BMD results. This will give the oncologist the opportunity to prescribe bisphosphonates

for prevention of bone lose prior to randomization in the study. Because of our communication with the oncologist at baseline, we feel confident that few women not taking bisphosphonates at baseline would initiate them during the trial. However, if a participant does initiate bisphosphonates during the trial, then we will have her complete a DEXA scan immediately prior to starting the medication. However, if a participant is taking bisphosphonates at baseline, she may still be eligible for the study since examining the impact of exercise on arthralgia severity is not confounded by bisphosponate use.

Arm volume measurement by Perometer: Women who at risk for lymphedema due to axillary lymph node removal will have bilateral assessment of arm volume performed by a lymphedema specialist at Yale. From this assessment a determination will be made regarding need for provision of compression garments prior to enrolling in the exercise arm. The measurements will be repeated at 12 months, to evaluate the effect of exercise on lymphedema. The Perometer used infrared light to scan the arm, which is of no risk to the participant.

Anthropometrics*:* We will measure height and weight (at baseline, 6-, and 12-months), and calculate BMI. Height and weight measures will be performed, by research staff blinded to the participant's randomization group. Participants will be weighed in light indoor clothing, without shoes, rounding up to the nearest 0.1 kg; height will be measured in a standard manner, without shoes, using a stadiometer, rounding up to the nearest 0.1 cm. All measures will be performed and recorded twice in succession.

Endocrine-related QOL: QOL will be measured by self-report and reviewed by research staff blinded to the participant's randomization group, at all visits (baseline, , 6-, , and 12-months). QOL will be measured using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire (version 3), together with the endocrine symptom subscale (ES) questionnaire (FACT-B+ES) (29). The FACT-B is a 38-item questionnaire with six subscales assessing physical, social, emotional, and functional well-being, and additional concerns more specific to women with breast cancer. The ES was designed for use with the FACT-B and comprises 18 items (e.g., hot flashes, night sweats, weight gain). Participants indicate how true a statement has been for them over the past 7 days using a 5-point scale ranging from 0 (none at all) to 4 (very much). All items receive equal weighting.

Psychological outcomes: Validated measures will be used to assess the psychological outcomes at baseline, 6- and 12-months. **Self-efficacy** will be assessed using the Rosenberg Scale [80]. The scale was shown to be reliable in the Yale Exercise and Survivorship (YES) Study, with Cronbach's alpha of .91. **Depression** will be measured with the Centers for Epidemiological Studies Depression Scale [81] (CES-D). Cronbach's alpha was .87 for the YES Study. **Anxiety** will be measured using the 20-item State-Trait Anxiety Index [82] (STAI), which differentiates between transient anxiety ("state anxiety") and more long-standing anxiety ("trait anxiety"). Participants in the study will complete only the state anxiety scale (STAI-YI) as trait anxiety is not expected to be modifiable. Chronbach's alpha was .94 in the YES Study. Lastly, **Pain Coping Skills** will be measured via the Catastrophizing subscale of the Coping Strategies Questionnaire (CSQ) (83). The 6 items that comprise the Catastrophizing subscale are the same in the 1983 and 2004 versions of the CSQ, thus the most recent version (2004) will be used. Catastrophizing is a trait-like measure that is relatively stable across time.

Lymphedema: Data indicate supervised strength training does not result in incident or worsening of lymphedema, and may be a safe exercise modality for breast cancer survivors (84). Women who have had total axillary node dissection or a sentinel node biopsy (i.e. are at risk for lymphedema) will be assessed by a physiotherapist for lymphedema by the use of a Perometer at both baseline and 12 months. This instrument measures limb volume by infra red light. The procedure is quick and none invasive. Those women who are identified as having lymphedema will be assessed to ensure that they have appropriate compression garments prior to starting the exercise intervention (see above). Compression garments will be worn during strength training sessions to prevent occurrence or worsening of lymphedema. In

addition, for safety reasons, in women randomized to exercise, we will assess self-report of lymphedema symptoms, at baseline, 6- and 12-months, using a survey that has previously been shown to have a specificity of 0.90 and sensitivity ranging from 0.86 to 0.92 for diagnosing lymphedema (defined as difference in circumferences of greater than 2 cm) when compared to clinical assessment by a physical therapist with special training in lymphedema (85). Women who experience lymphedema will be referred to a lymphedema specialist.

Theory of Planned Behavior (TPB) and Transtheoretical Model (TTM): Prior to randomization, information on intention, attitude, perceived behavior control, and subjective norm will be collected via reliable and valid questionnaires drawn from Ajzen's TPB (86) and the TTM. Both of these theories will be used to guide our exercise program (see Section D.10 for more information). These questionnaires will be completed at baseline and 12 months.

Medical Record Abstraction and Physician Verification of Treatment Reports: To confirm therapy and other treatments, the following will be abstracted from medical records and Physician Verification of Treatment Reports: disease stage, tumor size, number of involved axillary lymph nodes, hormone receptor status, therapy and evidence of completion; surgery; adjuvant therapy (none, radiation therapy, chemotherapy, hormonal therapy); type of AI including start date and potential end date; radiation therapy site (residual breast tissue, chest wall, regional lymph nodes), and bisphosphonate use (start and end date).

Other covariates: Baseline and follow-up values for certain covariates will be determined by a standard questionnaire, to assess for confounding of study results. Factors to be included are: reproductive and menstrual history, diet, medication use; medical history, family history of breast and other specific cancers, type 2 diabetes, and history of tobacco. Lastly, if other clinical trials find new approaches to improve arthralgia and AI-associated side effects during our study, we will keep abreast of any new developments in research that may impact our endpoints, and collect relevant data to adjust for it.

Analgesic Use: A number of analgesics have been used for arthralgia; however, none of these has proven entirely satisfactory. Women enrolled in our trial will be permitted to take non-steroidal pain medications as needed. However, we will ask participants to complete a 48-hr recall of analgesic use immediately prior to the baseline, 6-, and 12-month assessment of arthralgia. We will examine if use of analgesics (including NSAIDS, acetaminophen, or COX-2 inhibitors) differs by randomization group at all visits, and if between-group differences exist, we will adjust for use of analgesics. We will also explore stratifying the results by analgesic use. These methods were employed in Dr. Hershman's studies of arthralgia.

Blood Draw, Processing, Storage, and Measures of Inflammation: Approximately 40 ml of fasting blood (> 12 hours) will be drawn at baseline, 6- and 12-months in a standardized fashion. Two 10-ml red-top tubes will be collected for serum, and a 10-ml light blue-top and 10-ml lavender-top will be collected for citrate and EDTA plasma. Technicians in the lab will centrifuge the samples at 2,000 rpm for 15 minutes at 4°C. Plasma and buffy coat will be separated and transferred into cryovials and labeled with freezer-proof labels with participant ID #s and date (no identifiers will be included). All specimens collected will be stored temporarily at 4°C during transportation or prior to delivery to the YCCI specimen storage facility, and then stored at -70 degrees C until it is time to analyze them. The specimens will be stored in an organized storage system with unique location identifiers based on freezer compartment number, rack number, box number, and slot number. The freezer is configured with beepers and dial-up alarm systems in the event of a power failure or change in temperature.

Pro-Inflammatory Markers: We will conduct baseline, 6- and 12-month hormone analyses to examine the effect of exercise on hormones. Three markers (IL-6, TNF-α, and CRP) will be measured in Dr. Herbert Yu's lab at Yale School of Medicine. We have previously measured these hormones in the Yale Exercise and Survivorship Study. CRP will be measured with direct chemiluminescent immunoassay on the Immulite analyzer (Diagnostic Products Corporation (DPC, Los Angeles, CA). For TNF-α and IL-6, enzyme-linked immunosorbent assays (ELISAs) will be performed, using kits from R&D (Minneapolis, MN). Each woman's baseline and follow-up samples will be used in the same batch, and an equal number of intervention and control samples will also be included in the same batch. Appropriate quality control samples (low and

high levels) will be used to monitor the reliability of each assay. Each plate will measure 40 samples and include two sets of quality control (QC) samples. One set of the QC is internal QC that is provided in each kit. Any assay with its internal QC values out of the suggested range will be disregarded and the assay will be repeated. The second set of QC is external QC purchased from a different commercial source, which provides the QC for immunoassay analysis of serum or plasma samples. The results of external QC will be analyzed after all measurements are completed. Plates with external QC values greater or less than 2 standard deviation of the mean QC will be repeated. Also, in each assay run, samples with greater than 20% of coefficient of variation in their duplicated results will be repeated. Blind duplicates are also included in and between batches to estimate coefficient of variations.

Additional markers: We will examine the effect of the intervention vs. usual care on novel serum biomarkers associated with breast cancer, including lipid profile, IGF-1, metabolites, sex hormones, and telomere length.

Table D.2: Study Measurements

Measure	Baseline	3 Months	6 Months	9 Months	12 Months
Medical history and covariates	X	X	X	X	X
Physical Activity	X	X	X	X	X
VO2max	X				X
Perometer test	X				X
Grip Strength Testing	X		X		X
Muscular Strength Testing (exercisers only)	X	X	X	X	X
Height and Weight	X		X		X
DEXA Scan	X		X		X
Blood Draw	X		X		X
Psychological Measures	X	X	X	X	X
Arthralgia (pressure test$)	X$	X	X	X	X$
Endocrine-related QOL	X		X		X
Lymphedema	X	X	X	X	X
TPB and TTM	X				X
Physician Verification of Treatment	X				

D.9. 6-month intervention study. Questionnaires Information will be collected on medical history and health habits via a standard questionnaire administered at baseline, 3-, and 6-months. Specific health habits related to calcium and vitamin D intake and supplementation, chronic corticosteroid use, and alcohol consumption will be included. A screening questionnaire assessing eligibility criteria and any co morbidities will also be administered during a screening phone call. See D.9 for questionnaire descriptions.

Blood Draw, Processing, Storage, and Measures of Inflammation: Approximately 40 ml of **f**asting blood (> 12 hours) will be drawn at baseline and 6-months in a standardized fashion.

Dual Energy X-Ray Absorptiometry (DEXA) scans*:* DEXA is the gold standard measure of assessing bone density, osteopenia, osteoporosis, and body fat (79). DEXA scans will be performed at baseline and 6-months.

Lymphedema: Women who have had total axillary node dissection or a sentinel node biopsy (i.e. are at risk for lymphedema) will be assessed by a physiotherapist for lymphedema by the use of a Perometer at both baseline and 6 months.

D.10. Exercise Intervention: The exercise intervention group will receive social, behavioral support and research staff contact time to encourage them to increase their activity level to include twice weekly strength-training sessions and 150 min of walking/week (e.g., three 50-min walking sessions or five 30-min walking sessions) over 12 months. We chose a frequency of 2 weekly strength sessions because a review of prior strength training studies showed two times per week was sufficient to observe improvements in BMD (28,29). We also included a walking program because research has consistently shown walking being associated with weight maintenance and fat loss and QOL. Some trials have observed walking being associated with improvements in Lean Body Mass, but not Bone Mass Density. Furthermore, ACS and NCI currently recommend 150 min/wk of moderate-intensity physical activity for women diagnosed with breast cancer. If we observe a benefit in the proposed trial, future trials could examine the role of walking alone or strength training alone (2-arm or 4-arm trial) on AI-side effects with varying intensities, frequencies, and study durations.

Strength Training Sessions: Each strength training session will take ~60 minutes and will begin with a warm-up on a treadmill for 5 minutes followed by a stretching exercise for each of the major muscle groups to be worked during strength training. Participants will also do stretching at the end of each session, for injury prevention. Nine common strength-training exercises will be performed using variable resistance machines and free weights (for muscles of the chest, back, shoulders, quadriceps, hamstrings, and gluteals, as well as biceps and triceps). We will use the protocol developed by Katie Schmitz and colleagues. Their protocol was used in a pilot trial of strength training on lymphedema and is currently being used in a larger scale trial of strength training and lymphedema in breast cancer survivors (84). The protocol for determining resistance will differ for the upper versus the lower body. For the upper body, participants will start with no weight or 1/2 pound wrist weights for each exercise. If there are no changes in symptoms or onset of lymphedema-related symptoms by the next session, the weight will be increased by 1/2 pound increments. If there is any worsening/onset of symptoms, the exercise thought to be associated with the symptoms will be skipped, or a lighter weight will be used, until the symptoms have cleared up. In Schmitz et al's pilot study, most women found this conservative progression to be too slow and chose to increase the weights by 1-2 pounds from session to session (84). However, we will again start with a very slow progression, to be cautious. For the lower body, a standard progressive strength training approach will be used in which participants will lift the most weight they can lift in each exercise eight to ten times in each set of repetitions. Participants will build up to three sets per exercise over the first 2-3 weeks of exercise. Substitute exercises will be used if injuries or excessive soreness occur, or if there are range of motion limitations that preclude performing a specific exercise. For the first three months, the protocol for increasing weight on each exercise is as follows: after two sessions during which a participant lifted the same weight 10 times during each completed set, the weight will be increased by the smallest possible increment. If the higher weight is lifted at least eight times on the first set, and six times on the second set, additional set(s) will be attempted with the higher weight. Otherwise, the weight will revert to the amount lifted in the previous session. For the latter nine months, participants will increase the weight after 4 sessions during which the participant lifted the same weight for 10, 10, and 12 repetitions for sets 1, 2, and 3, respectively.
/Health Clubs to Conduct the Strength Training Exercise Sessions: The trainer and participant will meet at the gym weekly (in small groups of 3-5 participants) during designated times. Based on the YES Study, we anticipate only needing to recruit from five hospitals in CT (Yale-New Haven Hospital, St Raphael's Hospital, St. Vincent's Hospital, Bridgeport Hospital and Greenwich Hospital) which are within a relatively short distance of each other and will therefore only need to use a few gyms in those locations to conduct the intervention. Participants will be provided with 12-month memberships to these gyms. This approach was successfully used in the YES Study. Adherence to the intervention was high, 82% of participants adhered to at least 80% of the prescribed amount of exercise.

Walking Intervention: The participants will also be required to walk for a total of 150 min/week (the current PA recommendation (87)), whether it be at the health club or in their

neighborhood. Thus, we will work with each exerciser individually to find out what exercise opportunities exist in their neighborhood. Exercise will start at 50% of maximal heart rate (determined from VO2max testing) and will be gradually increased in accordance with American College of Sports Medicine guidelines to approximately 60-80 % of maximal heart rate. Heart rate will be electronically monitored with high/low pulse rate alarms individually set for each subject. Participants will gradually work up to exercising 150 min per week. The first month, three times per week of exercise will be prescribed. The second month, four times per week of exercise will be prescribed, and by the end of the second month, five days per week of exercise will be prescribed.

Recording of Strength and Walking Exercise Sessions: Following each strength and walking exercise session, subjects will complete their physical activity log. The logs will be turned in weekly to the Exercise Trainer, who will review the log in the presence of the participant. If 2 days of strength training and 150 min/wk of walking were not performed in the previous week, the trainer and participant will discuss the barriers experienced by the participant.

Theory of Planned Behavior: Ajzen's theory of planned behavior is a validated theoretical model that has been used to study exercise behaviors in breast cancer survivors (88). Ajzen's theory of planned behavior proposes that intention is the immediate determinant of behavior because it reflects the person's level of motivation and desire to exert effort. In turn, intention is thought to be determined by three independent constructs: attitude, subjective norm, and perceived behavioral control. Perceived behavioral control is defined as the perceived ease or difficulty of performing the behavior, and it may directly predict behavior if it is an accurate reflection of actual control. Attitude is viewed as a positive or negative evaluation of performing the behavior (e.g., good or bad), and subjective norm captures the perceived social pressure that individuals may feel to perform or not perform the behavior. The theory of planned behavior therefore proposes that (a) people will perform a behavior when they intend to do so and have the necessary control over it, and (b) people will intend to perform a behavior when they evaluate it positively, believe that important others think they should perform it, and perceive it to be under their own control. The theory of planned behavior has been used to understand exercise behavior in cancer survivors (62). These studies have provided evidence that this theory may be a useful model for understanding exercise behavior. Prior to randomization, participants will complete the Theory of Planned Behavior questionnaire. We will tailor the intervention based on the participants' responses to the questionnaire and their level of intention. Specifically, participants assigned to the exercise arm who have weaker intentions will be flagged and given more attention in terms of support and resources for behavior change. This will include highlighting possible incentives for exercise, proactively addressing any anticipated barriers to exercise, and securing social support from all participants and family members and their oncologist.

Summary and Benefits of our Exercise Intervention: Our exercise intervention combines multiple exercise approaches in an effort to maximize the number of participants who meet the study's physical activity goals. The mix of individual and group counseling and support was selected to reap the potential benefits of each approach. A major strength of the gym/health-club delivery approach is that participants will be able to exercise at times that are convenient to them (e.g., early mornings or evenings) and in all types of weather. The exercise trainers will also visit these sites each week during designated times, allowing them to directly observe the participant exercising. These visits will especially be utilized to assist women who are having difficulty in meeting weekly exercise goals. Individual contact is critical to retaining participants; thus each trainer will work individually with a participant throughout the study. In summary, we believe our intervention will be generalizable to most breast cancer survivors and can be implemented outside of a clinical trial. We anticipate that if our trial is successful and shows a favorable effect of exercise on AI-associated side effects, then oncologists will recommend exercise to most of their breast cancer patients. Currently, few oncologists recommend exercise to their patients because of a lack of data as to its benefit.

D.10.a 6-month intervention study: The exercise intervention will be ongoing for 6-months.

D.11. Attention Control Group (Also referred to as the Health Education Group): Immediately after randomization, participants in the Attention Control Group will be provided written information that emphasizes the importance of a healthy lifestyle. Participants will be encouraged to follow the NCI and ACS physical activity guidelines. This procedure was followed in our exercise trials, with no increase in physical activity levels observed at follow-up among women in the usual care group. Attention Control participants will also receive frequent contacts throughout the 12 month intervention. Each month, women randomized to attention control will be contacted by phone to discuss a health education topic of interest. Patient/health education has been shown to be a vital first step towards managing AI-induced side effects successfully and promoting adherence to AI treatment. Although the benefits of AI therapy may be explained to patients at the start of treatment, many do not comprehend fully the significance of total adherence throughout the course of treatment, which lasts several years. Generally, the reasons for non-adherence to treatment are varied, and include side effects, the benefits not being obvious immediately, an unwillingness of patients to accept that they need further treatment, and the acquisition of false or conflicting information from non-medical sources such as the media, family or friends. Advising patients that AI-associated side effects are common could mean they are more likely to approach their physician if symptoms arise, rather than ceasing their AI treatment without further medical consultation. We will develop monthly handouts that will be discussed at the phone contact. Health education topics that focus on issues relevant to women taking AIs, and breast cancer survivors in general will be included. Examples of topics are: 1) Bone health, 2) Lymphedema 3) Nutritional Guidelines. Exercisers will also receive the monthly handouts. Participants in both groups will also receive quarterly newsletters about the study and incentives for complying to study goals.

At the end of the intervention, attention control participants will receive a one-on-one sessions with one of our exercise trainers and a personalized exercise prescription, as well as any additional handouts given to the exercise group. Lastly, upon completion of the 12-month intervention, both control participants and exercise participants will be given information on survivorship clinics and other survivorship resources in Connecticut.

D.10.a 6-month intervention study: The Attention Control participants will also receive frequent contacts throughout the 6 month intervention. At the end of the 6-month intervention, attention control participants will receive a one-on-one sessions with one of our exercise trainers and a personalized exercise prescription, as well as any additional handouts given to the exercise group. Lastly, upon completion of the 6-month intervention, both control participants and exercise participants will be given information on survivorship clinics and other survivorship resources in Connecticut.

D.12. Data Processing, Storage, and Confidentiality: We will use a Web-based clinical study data management system that is located on a secure server at Yale University to store and manage study data. Only Dr. Irwin and her staff will have access to the database. Access will be by password protected.

D.13. Quality Assurance: Specific Quality Assurance procedures will include: 1) Development of and continuous updating of a detailed protocol and procedures manual; 2) Careful and systematic training of staff on performance of clinic measures, interviewing, and other procedures; 3) Reliability study: 10% repeat measures for all forms and measures; and 4) Range and consistency checks on data collection forms. All staff collecting data will be required to attend annual, one-day training sessions, conducted by the PIs, to review implementation of the study protocol. All staff collecting data will be instructed to be conversant with the study's protocol and all intervention manuals. The interim monitoring reports will be reviewed by the biostatistican and Data Safety and Monitoring Committee on a semi-annual basis. Additionally, we will discuss with the participants, at baseline and all follow-up visits, the importance of

"partnering in research." Participants will be told that complete, accurate, and timely reports are critical to the trial's success.

D.14. Statistical Analyses: Patients will be grouped according to the intention-to-treat philosophy in which all randomized participants will be analyzed according to their intervention assignment at randomization, regardless of compliance or adherence to the study. To examine the effect of the intervention on severity of arthralgia, BMD, QOL, and mediators/mechanisms of exercise on arthralgia, we will perform Analysis of Covariance (ANCOVA), with each woman's change in outcome (final value – baseline) modeled as a function of treatment with a covariate included for the baseline value. Given arthralgia is assessed with three measures (one measure for upper body, one measure for lower body and one measure assessing recent (past 7 days), we will examine the effect of exercise on each arthralgia measure. It is not common for studies of fibromyalgia or arthritis to create a latent variable that combines the three questionnaires, so to be consistent with the literature, we do not expect to do this in our study. Mixed effects models for correlated outcomes will also be used to model the data collected on the absolute change in the outcome measures using all follow-up time-points. However, our primary time points are baseline and 12-months where we will use ANCOVA to examine the change in arthralgia severity by randomization group. However, we will also examine if there is a trend in the change in arthralgia severity by including the 3-, 6-, and 9-month results. We hypothesize that change in arthralgia severity will occur in a linear fashion with a beneficial effect of exercise on arthralgia severity at 3 months, but an even stronger effect at follow up visits. Age, type of AI use, adjuvant treatment, disease stage, and BMI may be included as covariates in the models, as well as use of analgesics and calcium and vitamin D intake and supplementation. Specifically, we will examine if use of analgesics (including NSAIDS, acetaminophen, or COX-2 inhibitors) differs by randomization group at all visits, and if between-group differences exist, we will adjust for use of analgesics. We will also explore stratifying the results by analgesic use. Adherence will also be used as a covariate in secondary analyses. Two-sided tests will be used for significance.

Although we do not anticipate an appreciable number of lost-to-follow-up because of our plan for tracking participants, the impact of missing data will be determined by comparing results of complete case analysis to mixed model analyses using all available data, which assumes missing data are missing at random (MAR). Under the MAR missing data mechanism, the probability of lost-to-follow-up depends only on the observed data. Non-random or informative lost-to-follow-up occurs when missing data are dependent on the unobserved values. If differential loss to follow-up is observed, sensitivity analyses using methods for MNAR data such as selection models will be considered.

In regards to the potential for nonadherence to AI, truncated time intervals could be used. At baseline we will require that women adhere to the AI for the study duration. We feel that because women will have been taking AIs for at least 6 months prior to enrolling in the study, as well as experiencing at least mild arthralgia, they will be quite familiar with some of the negative side effects of AIs; thus, we hope that they will know if they are capable of continuing the AI for an additional year. However, if the participant is experiencing severe side effects and can no longer adhere to taking the AI, we will ask that she complete the post-intervention assessments immediately prior to discontinuing AI use. Thus, for the anticipated 10% of women that may discontinue AIs (10% rather than 20% because previous studies have shown that health education (our attention control intervention) is associated with improved adherence), truncated time intervals could be used. However, given that we have five data collection time points, our mixed modeling will also allow us to have observations at follow up time points.

D.15. Power and Sample Size Considerations: Hershman and colleagues recently published a trial of acupuncture for the treatment of arthralgia. Their primary objective was to examine the effect of acupuncture on decreasing arthralgia pain (measured by the reliable and valid Brief Pain Inventory (BPI) worst pain item). They observed a clinically meaningful 2-point decrease in arthralgia pain (baseline mean = 5.3 + 2.3, post-intervention mean = 3.3 + 2.3) ($p = .008$). If we power our proposed study to detect a conservative difference of 1.5 in the worst pain score, then we need to recruit 60 women per group to have 90% power at the 0.05 significance level.

On the BPI-Short Form worst pain item, participants rate pain on an 11-point scale, with patients classified as having mild symptoms if they report a score of 1 to 4, moderate symptoms if they report a score of 5 to 7, and severe symptoms if the score is 8 or more. Thus, a reduction of 1.5 (~14% decrease) is considered clinically meaningful. We will recruit 60 women per group, plus an additional 30% (i.e., 20% and 10% to account for potential drop-outs (exercisers who do little exercise and cross over so that they have no effect of exercise at all) and drop-ins (attention controls who do so much exercise that they have the same effect of exercise as those randomized to the exercise group or drop out of the study), respectively) for a sample size of N = 170. We will also increase the sample size by ~5% (n = 10 for a total N = 180) for adjustment of the stratification variables (i.e., chemotherapy and BMI) assuming they account for 10% of the variation in the outcome. This stratified randomization is likely to reduce the residual error of the model, thus increasing the overall trial efficacy. An N = 180 will also give us at least 80% power at the 5% significance level to detect clinically meaningful between group differences of 5% in LBM, QOL, cardiorespiratory fitness, body weight and fat, muscular strength, grip strength, pro-inflammatory markers, and psychological outcomes. Effect sizes and standard deviations for all the mediators come from our Yale Exercise and Survivorship Study.

Lastly, because some women may be taking bisphosphonates at baseline, we will have a reduced sample to examine the effect of exercise on BMD. Based on conversations with many breast oncologists, approximately 50% of our sample will be taking bisphosphonates at baseline. This is a very conservative estimate. Thus, with a sample size of 85 not taking bisphosphonates (or ~42 per group), we will have 80% power to detect a 4% difference in BMD between women randomized to exercise vs. attention control. Previously, we hypothesized a 2% between group difference based on our pilot data of aerobic exercise (mostly brisk walking) on BMD in breast cancer survivors. However, studies that have examined the impact of resistance training on BMD in healthy women have observed between group differences of ~5% (refer to section B). Since our trial will include a combination of both aerobic (weight-bearing physical activity) and resistance training, we hypothesize a 4% between group difference is feasible. A 4% between-group difference is clinically meaningful given that AI-related bone loss may occur at an accelerated rate (~2.6% bone loss per year with AI-use compared to ~1% bone loss per year after menopause), and decreases in BMD of 10% have been shown to approximately double the risk of fracture; thus, BMD increases of 4% can offer substantial preventative benefit.

D.16. Study Timeline: Data collection will take 3 years and will occur from month 6 through month 42. The total study is 4 years; thus allowing for 6 months lead up time and 6 months post-data collection for analyses and manuscript submission. Randomization of individuals will start at the beginning of month 6, and will continue until the end of month 30. Data entry and cleaning will be ongoing. Statistical analyses and report writing will begin around month 20 (manuscripts pertaining to study objectives and recruitment). We plan to present preliminary data (e.g. recruitment data) at conferences in Year 2 - 4 of the study.

D.17. Future Follow Up/Ancillary Studies: We plan on obtaining consent to contact the participants for future studies or ancillary studies. Future studies may involve examining the role of exercise on other potential AI-associated side effects such as lipid profiles. Data from some of the AI trials indicate a small increase in the incidence of cardiovascular adverse events. However, such reports arise from trials comparing AIs with tamoxifen, and consequently, the lipid-lowering and cardioprotective effects of tamoxifen may be driving these results (89). Lastly, we have not proposed to measure MRI-assessed tenosynovial changes, and whether changes are attenuated with exercise, because of the high cost of MRIs. However, we may pursue alternative sources of funding to conduct pre-and post-intervention MRI's on a subsample of study participants. Thus, we will be able to examine, in a small sample, the effect of exercise on MRI-assessed tenosynovial changes, as well as correlations between tenosynovial changes and arthralgia changes.

D.18. Strengths and Limitations: While our proposed trial has several strengths including the Investigators being experienced in recruiting and retaining breast cancer survivors into exercise trials, and assessment of arthralgia, QOL, and BMD, there are challenges associated with

conducting the proposed trial. One challenge is that it is unknown if exercise may improve or exacerbate AI-associated arthralgia. Exercise has been associated with decreasing estrogen concentrations in postmenopausal women, and the low levels of estrogen achieved with AIs contribute to arthralgia and bone loss. In one of our exercise trials in 173 healthy postmenopausal women, we observed an 8.2% reduction in free estradiol compared to no change in controls (p = .02) (90). However, since AIs decrease estrogens to 0, this is not likely to be an issue, and since exercise is associated with numerous other benefits, such as potential improvements in lymphedema (84), decreased breast cancer risk (91), recurrence and mortality (53,54), decreased cardiovascular disease (92), and improved quality of life (93), and because our pilot trial in 24 postmenopausal breast cancer survivors taking AIs showed a favorable effect of exercise on bodily pain (which may be a proxy of arthralgia), we feel that, if we monitor all participants closely, specifically in regards to arthralgia and bone metabolism, then this intervention may have a positive impact on arthralgia, bone metabolism, breast cancer recurrence and mortality, and quality of life. Participants will be stratified on presence or absence of pre-existing arthralgia. Investigators suggest that pre-existing arthralgia that is commonly experienced during menopause becomes more apparent or exacerbated by use of AIs. Thus, including this group of women will still provide novel and timely results related to the effect of exercise on arthralgia.

If our approach of implementing a moderate-intensity walking and strength training exercise program to attenuate side effects of AI therapy is not successful, we will still have vital information about arthralgia and other side effects of AI-use that can be used to inform us in designing future studies. One of the major strengths of the proposed study is that we will have important data on the severity of arthralgia and other AI-associated side effects. Few studies have examined arthralgia as a primary aim (thus, measurement of this side effect has been via questionnaires not designed to examine its severity). We believe that our approach (including our study design, eligibility criteria, recruitment methods, intervention, and assessment of outcomes) is not only innovative, but very timely (AIs just recently became regarded by many to be the standard of care for adjuvant therapy of hormone receptor positive breast cancer). In summary, we believe that the proposed study will provide important scientific and public health information on an exciting area of breast cancer survivorship, and is in keeping with the goals of the NCI and Office of Cancer Survivorship.

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

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

   Not applicable.

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

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

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

   iii. Who holds the IND or IDE?

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

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

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

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

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

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

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

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

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

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended? ☐ Yes ☐ No

If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

SECTION VII: HUMAN SUBJECTS

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

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

Recruitment will occur at Yale University and will take up to 3 years to complete. To identify potential participants, we will use strategies focused on tumor registries and community oncologists in addition to advertising in the community and on the internet. The tumor registry strategy involves the use of the Rapid Case Ascertainment (RCA) Shared Resource Service of the Yale Cancer Center. The RCA provides the PI with potential participants' names and their physician's names within two weeks of diagnosis. Physicians consent to contact their patients will be passive, that is the physician will be sent a list of women identified as potentially eligible for the study. If a physician has information about a specific patient regarding their participation in the study he/she will be asked to contact the office with this information. If we have had no response from the physician within 2 weeks of mailing the letter,we will mail an invitation letter to the participant, describing the study and telling her that a member of the research staff will be contacting her within a week to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, we will contact her treating physician (likely her oncologist) by mail asking for his/her permission to allow his/her patient to exercise. If we receive permission we will schedule a baseline visit. The community-oncology strategy involves presenting oncologists with a short synopsis of the study so that when permission is requested to contact the patient, the oncologist is already familiar with the study. Our goal is to recruit 121 breast cancer survivors over 2 years. We anticipate being able to recruit women diagnosed within the past 5 years (i.e., the time period when AIs became widely used). If ~ 2,720 breast cancer survivors are diagnosed per year in CT, we will be able to approach over 10,000 women for participating in our study to randomize 121 women (1.7%). Prior pilot studies of exercise interventions performed at Yale have yielded response rates of 6-40%.

While we only need to recruit 121 women, we will not necessarily approach all 10,000+ women diagnosed with breast cancer in Connecticut over the past 5 years. We will request that our rapid case ascertainment shared resource service of the Yale Cancer Center only provide us with the names of women diagnosed/treated 4 hospitals in CT that are in relatively close proximity, postmenopausal, and hormone receptor positive breast cancer. While, we are focusing on efficacy (i.e., internal validity) of exercise on improving AI-associated side effects rather than effectiveness (i.e., generalizability or external validity), we do feel that our results will be generalizable given that we are focusing on postmenopausal women taking AIs and experiencing arthralgia (i.e., a large majority of breast cancer survivors). A strength of the proposed study is our population-based recruitment strategy. Most studies use convenience-

based recruitment strategies (flyers, media) and are therefore unable to know the actual size of the target population.

We will use convenience based recruitment strategies in addition those strategies describe above. We plan to post flyers in doctors' offices, public places (e.g. libraries), explore using internet sites that target breast cancer survivors and have our phone number available when the study is reported in the media. If a woman self-refers and appears eligible, her doctor will be contacted to obtain permission for the woman to exercise.

We will collect information on the population approached (age, ethnicity, education, BMI, physical activity levels, disease stage), and will be able to make comparisons between the women enrolled and the women approached in regards to certain variables. However, as mentioned, while we feel our results will be generalizable to breast cancer survivors taking AIs and experiencing at least mild arthralgia, our trial will in fact be an efficacy trial. Therefore it is paramount that we focus on internal validity first by having tight control over study eligibility, assessments, and the intervention. If our results show a favorable effect of exercise on arthralgia severity, then future studies may examine the effectiveness of exercise on arthralgia.

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

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

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

For this trial, postmenopausal women diagnosed with Stage I-III breast cancer who are taking an aromatase inhibitor will be recruited to participate in an exercise trial on arthralgia, body composition, hormones, and quality of life. Women will have completed surgery and adjuvant treatment (i.e., radiation and/or chemotherapy), physically able to exercise, yet not currently exercising at recommended levels, and English speaking.

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

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

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

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

- Postmenopausal women (defined as the surgical or natural absence of menstrual cycles for at least 1 year prior to breast cancer diagnosis).
- 75 years or younger
- AJCC Stages I-IIIC Breast Cancer
- Taking an AI for at least 2 months
- Currently experiencing at least mild arthralgia (= or > 3 on the BPI) associated with AI use
- Physically able to exercise and physician consent to start an exercise program
- Sedentary activity pattern (< 90 mins/week of moderate-to-vigorous intensity sports activity) within the past year and low fitness level
- No more than one strength training session per week within the past year
- Agrees to be randomly assigned to either exercise or attention control
- Gives informed consent to participate in all study activities
- Able to come for baseline, 6-, and 12-month clinic visits and strength training sessions (6-month intervention study – able to come for baseline, 6-month clinic visits and strength training sessions).
- Mentally competent

Exclusion Criteria:

- Lymphedema with self reported 'flare up' in the past 4 months

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

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

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

SECTION VIII: CONSENT/ ASSENT PROCEDURES

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

   Melinda L. Irwin, study managers and research staff.

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

   We will mail an invitation letter to the participant, describing the study and telling her that a member of the research team will be contacting her within two weeks to tell her about the study and to solicit her interest and eligibility. If the participant is eligible and interested, we will contact her treating physician (likely her oncologist) by mail asking for his/her permission to allow his/her patient to exercise. If we receive permission a baseline visit appointment will

be scheduled for the next week at the research office in New Haven or at the participant's home. At the visit, the study will be described in detail again. If the participant is interested in participating and eligible, she will read and sign the informed consent form.

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

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

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

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

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

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

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

   ☒ **This section is not applicable to this research project**
   Waiver of consent: (No consent form from subjects will be obtained.)
   a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ No
   b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
   c. Why would the research be impracticable to conduct without the waiver?
   d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

   Waiver of **signed** consent: (Verbal consent from subjects will be obtained.)
   ☒ **This section is not applicable to this research project**
   a. Would the signed consent form be the only record linking the subject and the research? ☐ Yes ☐ No
   b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ Yes ☐ No
   OR
   c. Does the research pose greater than minimal risk? ☐ Yes ☐ No **AND**
   d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

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

☐ HIPAA Research Authorization Form

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

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

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

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

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

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

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

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

Assessment of the risk associated with participating in the study can be categorized as ***minimal***. All subjects will have a primary care physician or their oncologist or surgeon clear them for exercise. The Exercise Trainer will have weekly contact with each participant randomized to the exercise group. During this time, the Exercise Trainer will inquire about each participant's overall health and how she is adapting to the increased physical activity levels. The participants will be wearing heart rate monitors during their exercise sessions, and will be exercising within their heart rate range (50-70% maximal heart rate); participants will slowly progress up to 5 days, 30 mins per session at 50-70% maximal heart rate over the first 2 months; and they will be taught exercise principles by the Exercise Trainer.

The major risks of participating in this monitored exercise program include fatigue, muscle soreness, and possible joint or skeletal injury. These risks will be reduced by proper warm-up/cool down periods, conservative and individual exercise prescriptions and progression, and careful monitoring by an exercise physiologist. Any exercise program has a somewhat increased risk of a sudden heart attack. However, this risk is greatly reduced by having the physician, who has treated the participant since her cancer diagnosis, give consent for the

participant to start a monitored exercise program. The exercise physiologist will teach the participant techniques to minimize joint or muscle injury when she exercises. This study will not include sports or physical activities with a high probability of injury occurrence. Thus, the program will not include such high risk activities as bicycling outdoors, downhill skiing, or horseback riding. The participants can still do the activities they enjoy, but they will not be part of this research study. The type of activities recommended and prescribed will mostly be walking and stationary bicycling.

Strength training exercise has not been shown to be associated with lymphedema. As in the large randomized trial of strength training and lymphedema, women in our trial who have had a complete axillary node dissection or sentinel node biopsy will be seen by a physiotherapist prior to starting the exercise intervention and lymphedema will be assessed using a Perometer. The physiotherapist will to ensure that each woman has a prescription for appropriate compression garments to wear during the strength training sessions. A Perometer uses infrared light beams to assess limb volume and so is of minimal risk. Lymphedema will be monitored using self-report and women will be referred to a lymphedema specialist if they have symptoms of previously undiagnosed lymphedema or their condition worsens. . Payment for assessment and treatment will be the responsibility of the patient Women will be required to wear the prescribed compression garments during strength training sessions.

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

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

Risk associated with the treadmill test is minimal. The women will be monitored during the test by a trained technician and a physician will be present during all tests if medical intervention is required.

Risk associated with the pressure algometry test is minimal. There is a small risk of bruising and skin irritation and redness. The test will not be conducted at a specific body site (wrist or knee) if there has been a fracture in the last 6 months or a surgical procedure; if there is an open wound; surgical scars.

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.

Participants will complete the Centers for Epidemiological Studies Depression Scale CES-D at baseline, 6- and 12- months. If a participant scores more that 16 on the CSE-D, she will be contacted by one of the study staff and advised that she talk to her doctor regarding her thoughts and feelings.

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

Lastly, all staff have or will have taken the Human Investigations Training Course either online (through NIH) or in person through the Yale University School of Medicine. Dr. Melinda Irwin (Principal Investigator) will conduct data and safety reviews every six months. She will

evaluate the frequency and severity of any adverse events and determine if modifications to the protocol or consent form are required. A summary of the adverse events will be reported to the HIC every 12 months.

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

   Please see above.

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

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

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

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

4. **Confidentiality & Security of Data:**
   a. What protected health information about subjects will be collected and used for the research?

   Only names and contact information will be collected, but not used for research. This information will only be used to contact the participant for study participation, and then once enrolled, information will be used to contact the participant if she is missing an appointment and to conduct the monthly telephone calls in the health education group. However, we will take several precautions to protect confidential information. All data will be stored on a database

located on a password-protected secure server that is accessible only to the PI and her research team.

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

Data will be collected on forms that will then be data entered and stored on a password protected database located on a that is accessible only to the PI and her research team. Data Entry Security: Users can only gain access to the database through authorization by the Principal Investigator of specific privileges for a specific study. Multi-session log-ins by a single user are prohibited. Users must change passwords every 90 days.

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

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

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

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

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

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

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

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

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

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

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

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

N/A

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

N/A

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

The potential benefit of this study is the provision of new knowledge about ways to assist breast cancer survivors taking hormonal therapy. Collection of physical activity patterns and effect on side effects of hormone therapy and breast cancer biomarkers should provide information for cancer surgeons and oncologists, and physicians to help cancer survivors manage their conditions which may potentially reduce side effects and risk for recurrence. The benefits to the participants include better knowledge of changes in their physical activity habits, and an improvement in their cardiorespiratory fitness, cardiovascular risk, improved body composition and quality of life, and possibly a decreased risk of death.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

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

An alternative is not participating in the study.

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

Participants will learn the principles and techniques of how to exercise safely and at the appropriate intensity level. Those in the exercise group will receive this instruction from the exercise trainer for 12 months. Women randomized to exercise will be given a heart rate monitor to keep ($50) and also be given a 12-month health club membership (valued at $250). If a woman in the exercise group needs compression garments, her insurance will be billed for the cost of fitting the garments and the garments. If her insurance does not cover this cost or if she does not have insurance, the study will pay for these expenses. The costs for all study tests and procedures, including DEXA scans, treadmill test, lymphedema assessment and blood analysis will be provided free of charge. All participants will be given a pedometer to keep ($20). Parking costs for the baseline, 6- and 12-month clinic visit will be paid for by the study and women will be given a $20 gas card to help defray travel costs. Women will also receive a $50 Walmart gift certificate for completing the study.

6-month intervention study: Participants will learn the principles and techniques of how to exercise safely and at the appropriate intensity level. Those in the exercise group will receive this instruction from the exercise trainer for 6 months. Women randomized to exercise will be given a heart rate monitor to keep ($50) and also be given a 12-month health club membership (valued at $125). If a woman in the exercise group needs compression garments, her insurance will be billed for the cost of fitting the garments and the garments. If her insurance does not cover this cost or if she does not have insurance, the study will pay for these expenses.
The costs for all study tests and procedures, including DEXA scans, treadmill test, lymphedema assessment and blood analysis will be provided free of charge. All participants

will be given a pedometer to keep ($20). Parking costs for the baseline and 6- month clinic visit will be paid for by the study and women will be given a $20 gas card to help defray travel costs. Women will also receive a $50 Walmart gift certificate for completing the study.

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

   There is no cost associated with participation in this study.

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

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

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