A PHASE II SINGLE ARM ADAPTIVE WEIGHT LOSS STUDY IN WOMEN WITH EARLY STAGE BREAST CANCER

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1. SUMMARY

Excess body weight is a significant risk factor for many cancers, especially breast cancer. Obesity can affect survivorship and quality-of-life factors including sexual function, neuropathy, cardiotoxicity, chronic fatigue and lymphedema. In retrospective studies, patients with a history of or current breast cancer who are overweight or obese are at an increased risk of therapy-related morbidity, recurrence, and breast cancer-related mortality[1,2]. Most cancer guidelines recommend that breast cancer survivors who are overweight or obese lose weight and that those within a normal body mass index (BMI) maintain a stable body weight. The cornerstone of interventions to treat or prevent obesity includes lifestyle modification with diet and exercise; however, integration into clinical practice is challenging due to limitations with standardization and scalability.

Our collaborators from the Welch Center for Prevention, Epidemiology, and Clinical Research at the Johns Hopkins University have reported impressive and sustained weight loss in randomized controlled trials designated Practice-based Opportunities for Weight Reduction (POWER) in obese women with at least one cardiovascular risk factor using a remote-support weight loss intervention[3]. This remote-support weight loss intervention of the POWER study has been adapted in women with early breast cancer who are overweight or obese, designated POWER-remote, and demonstrated statistically significant weight loss of ≥5% body weight, compared to self-directed weight loss at 6 and 12 months[4]. Our recent evaluation of 6 months of the POWER intervention in breast cancer survivors found that 46% of women randomized to the POWER-remote arm were able to lose ≥5% of their baseline weight as compared to only 10.9% of women in the self-directed arm.

While some patients with early stage breast cancer are able to achieve significant clinically meaningful loss, the majority are unable to. The goal of this project is to evaluate whether weight loss in overweight/obese breast cancer survivors whose trajectory suggests unlikelihood of attaining clinically significant weight loss of ≥5% with behavioral intervention alone can be augmented with pharmacotherapy. Studies have shown that self-directed weight loss is generally not successful. Our POWER-remote study showed that 89.1% of women in the self-directed arm were not successful in weight loss. With the implementation of remote behavioral intervention, this value drops to 54% of women not being able to lose at least 5% of their weight. We will focus on this population of women, as they may be identified earlier (after 4-12 weeks of behavioral intervention). Success for this study will be measured by the rate of these women who are able to achieve weight loss with the adapted behavioral intervention with pharmacotherapy. As there are over 3 million breast cancer survivors in the US[5], many of whom are overweight/obese, underutilization of anti-obesity drugs may be a critical and neglected component of weight loss treatment.

We will evaluate the extent to which implementation of a chronic weight loss medication, Contrave® (Naltrexone/Bupropion), is associated with achieving ≥5% weight loss. All patients will receive the POWER-remote behavioral weight loss intervention (BWL) and have a behavioral coach for the duration of the 6 month study. During months 1-3, the behavioral coach will call weekly. From months 4-6, the behavioral coach will call monthly. At week 9, those who lose ≥5%, designated fast responders, will continue with BWL alone (FAST-BWL) while those

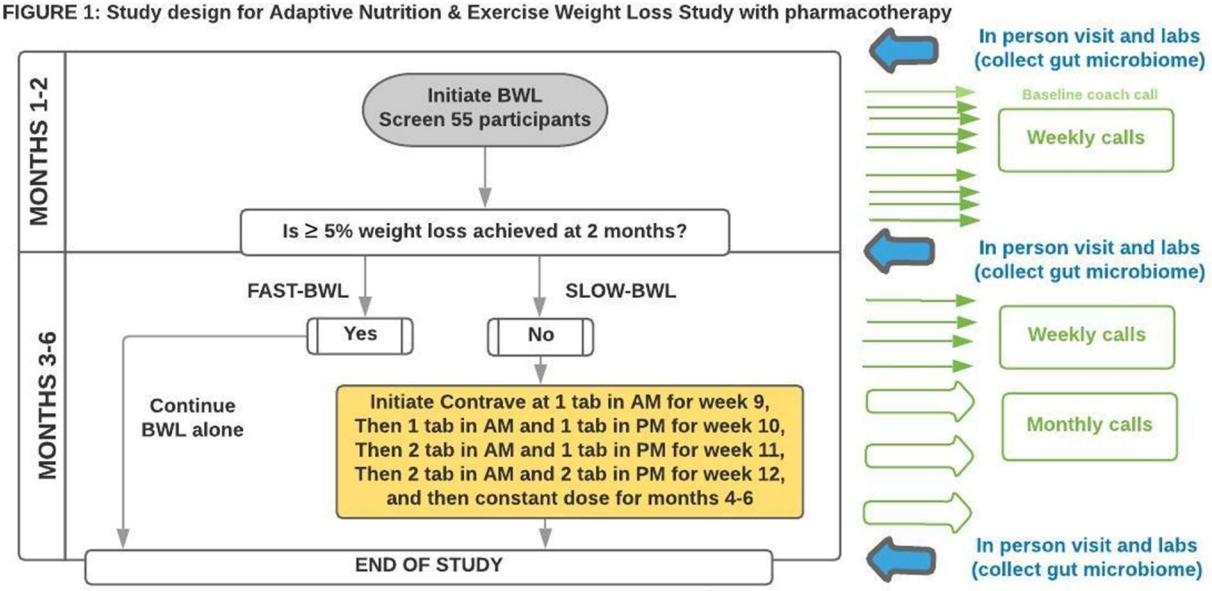
who lose <5%, designated slow responders, will continue BWL and initiate Contrave (SLOW-BWL). The SLOW-BWL arm will receive at least 16 weeks of Contrave (as per Federal Drug Administration [FDA] recommended administration) starting at week 9 and discontinue if ≥5% weight loss is not achieved at month 6. During month 3, all participants continue to have weekly calls with the behavioral coach and will be asked about symptoms, which may be related to initiation of pharmacotherapy; any symptoms are reported to the Protocol Chair for further evaluation. In addition to total weight loss, we will evaluate biomarkers associated with obesity, microbiome and cardiometabolic factors.

The ability of a diet and behavioral interventions to promote a more favorable microbiome profile, a lower BMI, and reduced levels of inflammatory cytokines, may help explain why vegetarian diets, and particularly vegan diets, seem to be protective against cancer growth in general and PC in particular. Our study, through its focus on inflammatory biomarkers, analysis of fecal microbiota, and traditional metabolic endpoints such as weight loss, adiposity, insulin resistance and hyperlipidemia, will help elucidate the complex interplay between metabolic disorders and inflammation in breast cancer survivors. Perhaps more importantly, we are confident that our study will offer breast cancer survivors a low-risk strategy to weight management, with tremendous potential for near-term impact on their quality of life and health outcomes. We will also assess certain genotypes to determine whether the effect of an adaptive weight loss intervention on biomarkers is greater in the patients who have a particular genotype (e.g. AA-*SOD2*). The potential increase in antioxidants in the adaptive weight loss intervention may enable certain patients with certain genotypes to gain greater benefit from the diet than others.

Our research will address a major gap in the literature that could potentially improve quality of life and cancer and non-cancer outcomes for obese breast cancer patients. While many studies have explored various interventions for weight loss in cancer survivors, to our knowledge none have explored the influence of weight loss pharmacotherapy in breast cancer survivors. Additionally, these medications have not been studied in the setting of use of hormonal therapy, such as tamoxifen or an aromatase inhibitor. The data will be used not only to assess the impact of weight loss and biomarker modulation but also to design definitive studies available to all overweight and obese women with breast cancer whom struggle to achieve clinically significant weight loss despite lifestyle intervention.

2. SCHEMA

FIGURE 1: Study design for Adaptive Nutrition & Exercise Weight Loss Study with pharmacotherapy



3. HYPOTHESIS

- In SLOW-BWL, adding Contrave at week 9 of a weight loss intervention may augment BWL and allow women to lose ≥5% of their baseline body weight at 6 months.
- In SLOW-BWL, weight loss of ⩾5% baseline body weight will be associated with changes in the following from baseline to 2 and 6 months:
  - reductions in fasting glucose, fasting insulin, total and low-density lipoprotein (LDL) cholesterol, triglycerides, leptin;
  - increases in high-density lipoprotein (HDL) cholesterol and adiponectin;
  - altered gut microbiome (decrease in the ratio of bacteroides and firmacutes); and
  - improved patient reported outcomes (PROs)
  - increased total lean mass, and decreased % fat mass and visceral fat
- Compared to women who are able to achieve at least 5% weight loss with 2 months of behavioral intervention alone, women who are unable to achieve ⩾5% weight loss with behavioral intervention alone may have identifiable baseline characteristics (i.e., cardiometabolic profile, obesity biomarker, microbiome composition or PROs) that may be predictors of whom may benefit from earlier initiation of pharmacotherapy.

4. OBJECTIVES

4.1 Primary Objectives

4.1.1 To assess the rate of SLOW-BWL patients attaining at least 5% weight loss of their baseline body weight at 6 months with the addition of Contrave to BWL at week 9.

4.2 Secondary Objectives

4.2.1 To compare cardiometabolic biomarkers (HbA1c, IGF 1, fasting glucose, fasting lipids, fasting insulin, adiponectin and leptin levels), microbiome composition, body composition, and PROs at 2 and 6 months to baseline levels among SLOW-BWL who achieve ⩾5% weight loss.

4.2.2 To compare cardiometabolic biomarkers, microbiome composition, body composition, and PROs at baseline of SLOW-BWL women who achieve ⩾5% weight loss versus the SLOW-BWL women who do not achieve 5% weight loss.

4.2.3 To compare the moderate to vigorous physical activity (MVPA) and daily steps at 2 and 6 months to baseline levels among SLOW-BWL who achieved ⩾5% weight loss vs the SLOW-BWL who did not achieve 5% weight loss.

4.3 Exploratory

4.3.1 To assess the proportion of women in the FAST-BWL arm who maintain ⩾5% weight loss at 6 months.

4.3.2 To describe baseline characteristics (cardiometabolic and obesity biomarkers, microbiome composition, PROs, demographics) of FAST-BWL vs SLOW-BWL, as well as participants who achieve ⩾5% weight loss at 6 months vs those who are unable to.

4.3.3 To assess prevalence of AA genotype of MnSOD in breast cancer survivors with excess weight and if a greater proportion of women with the AA genotype achieve ⩾5% weight loss and improvement in biomarkers at 6 months compared to the women who do not.

4.3.4 To determine if women who display the AA genotype of MnSOD and undergo addition of Contrave to BWL have greater weight loss compared to women who do not receive Contrave.

5. BACKGROUND AND RATIONALE

5.1 The Biology of Obesity and Breast Cancer

Studies have strongly suggested that excess body weight and weight gain may be a major risk factor for many cancers including breast cancer[6–8]. The biological relationship between obesity and breast oncogenesis is mediated by several pathways. Obesity has been associated with increased levels of inflammatory cytokines, for example interleukin 1β, interleukin 6, tumor necrosis factor α, and monocyte chemoattractant protein 1. Altered levels of these cytokines drive pro-proliferative pathways, such as angiogenesis, influx of macrophages, and anti-apoptotic pathways [9]. Another untoward effect of obesity is increased synthesis of estrogens from androgens via augmented aromatization of androstenedione in peripheral adipose tissue.

Breast carcinogenesis has also been associated with increased serum leptin levels and low adiponectin. Leptin is an adipocytokine synthesized by adipocytes and it acts as a satiety hormone at the hypothalamus level to reduce appetite and is paradoxically elevated in obese individuals [10]. High levels of leptin lead to concomitant activation of various oncogenic pathways resulting in increased tumor growth, angiogenesis and acquisition of a migratory and

invasive mesenchymal phenotype [11]. Adiponectin counters obesity by modulating glucose metabolism, increasing fatty acid oxidation and insulin sensitivity, and decreasing production of inflammatory cytokines.

Increased adiposity also increases circulating levels of insulin and insulin-like growth factor 1, which may also promote cell proliferation. Favorable changes in estrogens, sex hormone binding globulin, insulin, and leptin are observed in association with weight loss of at least 5% [12]. Furthermore, weight loss of at least 10% has been associated with modulation of serum and tissue biomarkers, such as Ki-67, adiponectin, adiponectin to leptin ratio, sex hormone binding globulin, estradiol, testosterone and insulin[13]. These biological data not only provide insight into how obesity can increase the risk of breast cancer, but suggests that weight loss may reverse some of these deleterious biological changes associated with obesity.

5.2 Obesity and Breast Cancer Outcomes

The four major cancer agencies (International Agency for Research on Cancer [IARC], American Cancer Society [ACS], American Institute for Cancer Research [AICR], and Center for Disease Control [CDC]) recommend that survivors maintain a stable body weight in the normal range and avoid weight gain[14]. Retrospective studies have shown that patients with breast cancer who are obese have an increased relative risk of recurrence by 40-50% and breast cancer-related mortality by 53-60% [1,2]. Obese women with hormone receptor positive operable breast cancer have inferior outcomes in terms of disease free survival (DFS) (Hazards Ratio [HR], 1.24; 95% confidence interval [CI], 1.06-1.46; $P = 0.0008$) and overall survival (OS) (HR, 1.37; 95% CI, 1.13-1.67; $P = 0.002$) in comparison to non-obese group [15]. Overall, approximately 15% of breast cancer cases in postmenopausal breast cancer survivors may be attributable to weight gain [16]. In premenopausal women, short-term weight gain may increase breast cancer risk although data are mixed [17].

In the Women's Intervention Nutrition Study (WINS), women with early stage breast cancer on a dietary intervention with clinically meaningful weight loss had 24% lower risk of relapse compared to those not receiving the intervention[18]. In the Women's Healthy Eating and Living (WHEL) study, dietary intervention did not lead to weight loss and did not reduce breast cancer recurrence[19]. These studies suggest that alteration in diet or activity alone may not be sufficient, and that greater loss is required to improve breast cancer-related outcomes[20]. While definitive data are pending, initial data suggest that weight management for improved cancer related outcomes is an important aspect of survivorship care.

To confirm the positive impact of weight loss on survival outcomes (such as DFS), a large randomized study has been designed and is actively accruing [21]. The Alliance for Clinical Trials in Oncology Breast Cancer Weight Loss trial (BWEL, NCT02750826) is testing the 10 year impact of a telephone weight loss program on invasive DFS in 3136 women with a BMI ≥ 27 kg/m^2 with recent diagnosis of stage II-III estrogen receptor positive or triple negative breast cancer [22].

5.3 Weight Gain in Breast Cancer

Chemotherapy associated weight gain is experienced by most patients during their first year of diagnosis [23]. There is greater weight gain among postmenopausal women receiving

chemotherapy than women receiving just surgery or surgery plus radiation, but not among premenopausal women or women who became postmenopausal after diagnosis. Studies have shown that women have decreased levels of physical activity after the diagnosis of breast cancer, which may contribute in part to weight gain. Moreover adjuvant chemotherapy may also decrease resting rates of metabolism [24]. Additionally, hormonal changes during menopause can affect metabolism and lead to weight gain[1,2].

Large studies have not demonstrated an association between hormone therapy and weight gain. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, comparing anastrozole and tamoxifen, there was no significant difference in weight gain between the two therapies (median weight gain 1.4 kg (SD 3.9) versus 1.5 kg (SD 4.0), respectively P = 0.4)[25]. Recent data, from the Exercise and Nutrition to Enhance Good Health for You (ENERGY) trial, however, suggests that patients receiving an AI may be less likely to gain weight than those on a selective estrogen receptor modulator (OR = 0.54, 95 % CI 0.31–0.93)[26]. While these data may be conflicting, and there are numerous other variables such as chemotherapy and menopausal status that can affect weight gain, there is insufficient evidence to suggest endocrine agents in general cause a significant amount of weight gain, and efforts at weight management should be directed at lifestyle changes rather than therapy discontinuation.

5.4 Effects of Obesity on Quality of Life in Breast Cancer

Obesity at and following breast cancer diagnosis is significantly associated with poor health-related quality of life and functional health, and may increase the risk of adverse treatment effects.

Obesity can affect body image, sexual and genitourinary function in breast cancer survivors. A cross-sectional survey of 255 patients at least one year from surgery showed that obese and overweight women reported more appearance dissatisfaction (18.1 and 13.0%) than normal weight women (4.1%) (p=0.02). A greater proportion of overweight women (94.7%) reported their chest played an important role in intimacy before and after surgery as compared to normal weight women (80.6%), but a postoperative decline in the importance of this role was observed in all groups (overweight p=0.01, normal weight p<0.001) [27]. Furthermore, being overweight or obese at baseline was associated with more problems with urinary incontinence and tendency to nap, and with poorer physical functioning and bodily pain (versus BMI<25 kg/m^2) [28].

Neuropathy is more common in patients who are obese. Chemotherapy-induced peripheral neuropathy (CIPN) has been reported in up to 44% of patients receiving chemotherapy, particularly taxanes [29]. Higher BMI is associated with a higher incidence of neuropathy, with studies demonstrating a prevalence of 48.4% in participants with normal weight, 60.2% in overweight participants, and 66.7% in obese participants. Compared with women of normal weight, being obese was associated with an increased risk of CIPN (adjusted OR 1.94, 95 % CI: 1.03-3.65) [30]. Increased neuropathy was significantly more likely to occur in overweight compared with normal weight patients receiving taxane treatment at 24 months and less likely to occur in patients with high moderate-to-vigorous physical activity compared with those with lower activity at 24 months [31]. While studies have not shown that weight loss can reverse neuropathy, these data suggest that physical activity may help decrease neuropathy.

Because obesity is already a strong risk factor for cardiovascular disease, cancer treatment in obese patients can further increase overall risk for adverse cardiac effects [32]. A recent meta-analysis suggests that being overweight or obese may be risk factors for cardiotoxicity from anthracyclines, especially in sequence with trastuzumab [33]. Other studies have found obesity to be associated with an increased risk of cardiac dysfunction in women using trastuzumab [34]. Additionally, in elderly patients (over 65 years), obesity is an independent risk factor for trastuzumab-related cardiac toxicity [35].

About one third of breast cancer survivors have chronic fatigue and about one fourth will have persistent fatigue after two years [36]. Although the development of fatigue in breast cancer patients seems largely impacted by cancer therapy, the long-term persistence of fatigue is related to preexisting medical conditions and lifestyle factors. Higher BMI at baseline is significantly associated with increased physical fatigue during and after cancer treatment [37]. The Mammary carcinoma Risk factor Investigation (MARIE) study demonstrated that both physically inactive lifestyle and obesity were associated with persistent physical fatigue, independent of chemotherapy and radiation [38]. In a study of patients who were overweight or obese, fatigue after chemotherapy lower in an exercise group versus a non-exercise group [39]. Higher BMI, associated with greater tendencies to catastrophize about fatigue and amplify physical symptoms, was predictive of fatigue at beyond nine months [40]. These studies demonstrate the importance of an ideal body weight as chronic fatigue is associated with emotional distress and limits function and willingness to exercise.

Lymphedema is more common in obese patients. Cancer treatments such as lymph node dissection and radiotherapy can damage the lymphatic drainage routes, leading to fluid build-up, discomfort, and reduced mobility and function. Excess adiposity may increase risk of lymphedema by increased inflammation, added stress to the lymphatic system, or slower healing times after surgery [41]. Data suggests that obesity increases risk of lymphedema after treatment for breast cancer. Prospective studies have reported statistically significantly higher lymphedema risk for obese compared to normal-weight women (OR 2.48; 95% CI 1.05–5.84) [42]. Breast cancer survivors who were obese at the time of breast cancer treatment were approximately 3.6 times more likely to develop lymphedema at 6 months after diagnosis than those who were not obese [43]. In a pilot study among overweight breast cancer survivors, a 12 week diet intervention resulted in a significant reduction in BMI and swollen arm volume (reduced from 24% to 15%, p=0.02) [44].

5.5 Predictors of Successful Weight Loss

Initial weight loss response at 4-12 weeks predicts weight loss at 1 year and afterward[45–48]. In the Look AHEAD trial, individuals with diabetes who lost 5% of initial weight at 2 months were 7.9 times more likely to achieve 10% weight loss at 12 months than those whom could not achieve 5% weight loss at 2 months[47]. At one year, the arm with intensive lifestyle intervention lost 8.6% of initial weight and the support arm lost 0.7%. Of 2,303 patients, over 55% were slow responders (unable to lose >5% of initial weight at 2 months) and only 18.5% of patients in this group were able to achieve 10% weight loss at 12 months. Of those whom were fast responders (losing >5% initial weight at 2 months), 63.8% succeeded in losing 10% weight at 12 months.

Interestingly, weight loss of ≥10% has been associated with greater improvement in physical function as measured by physical performance test and functional status questionairre[49]. A substudy of women in this trial demonstrates that women tend to lose less weight than men at one year in the intensive lifestyle intervention group versus the diabetes support and education group[50]. Unfortunately, many patients are unable to achieve clinically significant weight loss of ≥5% and regardless of initial weight loss success, sustaining long term weight loss is difficult[51,52]. Thus, new interventions that will allow all individuals to achieve optimal and sustained weight loss are urgently needed.

5.6 Weight Loss Interventions for Breast Cancer Survivors

Table 1. Studies of Remotely Supported Weight Loss Interventions with ≥ 100 Participants with Early-Stage Breast Cancer who were Overweight/Obese

Study	**Breast Cancer Subtype**	**Intervention Arms (Duration)**	**Mean Weight Changes***
Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer (LISA)[53], 2014	HR+, 98%–99% HER2+, 8%–14%	1. Remote 2. Mailed information (24 mo)	1. −3.1 kg 2. −0.3 kg
Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) study[54], 2015	NR	1. Remote (w/group program) 2. Usual care (24 mo)	1. −3.7% 2. −1.3%
Sex Hormones and Physical Exercise (SHAPE-2) study[55], 2015	NR	1. Mainly calorie restriction 2. Mainly exercise 3. Usual care (4 mo)	1. −4.95 kg 2. −5.58 kg 3. +0.06 kg
Christifano et al[56], 2016	NR	Single arm, Remote (6 mo)	−13.2%
Fazzino et a[57], 2017	HR+, 73%	Single arm, Remote (w/Fitbit) (6 mo)	−13.9%
Hormones and Physical Exercise (HOPE) study[58], 2017	All HR+	1. Supervised 2. Remote (12 months)	1. BMI, −0.73 kg/m^2 2. BMI, −0.17 kg/m^2
Dieli-Conwright et al[59], 2018	HR+, 84%	1. Supervised 2. Usual care (w/Fitbit) (4 mo)	1. −4 kg 2. +0.5 kg

*All values are statistically significant.
BMI = body mass index; HER2 = human epidermal growth factor receptor; HR = hormone receptor; NR = not reported.

Studies of overweight and obese patients in a primary care setting shows that intensive, face-to-face behavioral counseling for at least 3 months with at least 6 months follow up can induce clinically meaningful weight loss [60]. Since limitations of in-person weight loss interventions are constraints in time and cost, remote interventions with similar efficacy are more scalable with real-world integration.

At Johns Hopkins, the POWER trial in obese individuals with at least one cardiovascular risk factor (n=415) demonstrated equivalent weight loss outcomes between in person coaching and a remote-support weight loss intervention (telephone calls by a health coach, Fitbits to assess physical activity, self-directed dietary and activity monitoring, and web-based learning modules) [3]. Participants were recruited from six primary care practices in Baltimore, Maryland and 63.6% were women and the mean age was 54.0 years. One intervention provided patients with weight-loss support remotely through the telephone, a study-specific Web site, and e-mail. The other intervention provided in-person support during group and individual sessions, along with the three remote means of support. There was also a control group in which weight loss was self-directed. In these two behavioral interventions, one delivered with in-person support and the other delivered remotely without face-to-face contact between participants and coaches, obese patients achieved and sustained clinically significant weight loss over a period of 24 months. At 6 months, 52% of participants in the intervention group and 14% of participants in the control group achieved ≥5% weight loss.

An adaption of this remote intervention was implemented in a study of overweight or obese breast cancer survivors in a phase II single-blind trial from 2013-2015, which aimed to compare a remotely-delivered weight loss intervention (POWER-remote) to self-directed weight loss. At 6 months, 46% of women randomized to the POWER-remote arm were able to lose ≥5% of their baseline weight as compared to only 10.9% of women in the self-directed arm[4]. At 12 months, 38% of patients were able to achieve 5% weight loss with the intervention versus 13% in the self-directed arm. Weight loss correlated with significant decreases in leptin, and favorable modulation of inflammatory cytokines and lipid profiles.

The POWER-remote is a feasible and scalable behavioral weight loss intervention. While almost half of patients were able to achieve ≥5% weight loss at 6 months with behavior intervention, only half of these women were able to maintain this at 12 months. Given evidence in the obese population about earlier predictors of sustainable weight loss, we plan to identify women who are "SLOW" responders to POWER-remote (unable to achieve at least 5% weight loss at 2 months) and to implement pharmacotherapy to augment lifestyle modifications. We hope to discover novel strategies to help breast cancer survivors treat obesity and to potentially improve non-cancer and cancer outcomes.

5.7 Biomarkers and Genes

Prior studies have demonstrated that weight loss is associated with decreased all-cause mortality[61], decreased prevalence of prediabetes and cardiovascular disease[62], decreased glycemic parameters, decreased fasting lipids and decreased biomarkers such as adiponectin, insulin, IGF-1, leptin[4,59]. Weight loss studies have also demonstrated alteration in the gut microbiome which may be mediated by epigenetic modulation of gene activity in cancer[63].

Oxidative damage has been implicated in the pathogenesis of many chronic progressive diseases, such as cancer and obesity.[64–67] Mn superoxide dismutase (MnSOD) is the main enzyme responsible for scavenging reactive oxygen species (ROS) in mitochondrial oxidative stress, and catalyzing the dismutation of the superoxide radical (O_2^-) to H_2O_2.[68,69] There are three known forms of SOD: (*a*) the cytosolic copper/zinc SOD; (*b*) the extracellular copper/zinc SOD; and (*c*)

the mitochondrial MnSOD.[70] MnSOD is synthesized in the cytosol and posttranscriptionally modified for transport into the mitochondrion. In mice, MnSOD deletion in adipocytes is protective against weight gain and insulin resistance through the stimulation of mitochondrial function and biogenesis, thereby allowing the clearance of fatty acids.[71] However, other studies suggest a positive association between MnSOD polymorphism and obesity.[72]

Low MnSOD activity, depending on *SOD2* genetic polymorphisms, may contribute to the breast carcinogenesis and survival.[35,73,74] The most commonly studied polymorphism of the *SOD2* gene is a single nucleotide substitution of C to T at the second nucleotide of codon 16 of the *SOD2* gene, encoding an amino acid substitution from alanine to valine at position 9 of the mitochondrial targeting sequence of the mature protein. MnSOD genotypes containing the variant A allele were found to be associated with a 1.5 fold increased risk of breast cancer compared with the homozygous wildtype genotype.[75] In fact, increased expression of *MnSOD* has been found to suppress the malignant phenotype of human breast cancer cells suggesting that *MnSOD* is a tumour suppressor gene in human breast cancer.[76] However, some studies show that a *MnSOD* variant allele appears to be associated with an improved recurrence-free survival in breast cancer patients.[77]

Levels of oxidative damage vary with the consumption of meats, vegetables, and fruits.[78] Risk of breast cancer was greatest among women who consumed lower amounts of dietary antioxidants and was minimal among high consumers indicates that a diet rich in sources of antioxidants may minimize the deleterious effects of the *MnSOD* polymorphism.[79,80]

5.8 Chronic Weight Loss Medications

A domain that may offer enhanced behavioral approaches to weight loss includes pharmacotherapy[81]. Anti-obesity drugs, via reduction of hunger and food cravings and enhancement of satiety, help patients to limit the amount of food they eat, thereby increasing their adherence to the prescribed diet plan[81]. Based on data demonstrating weight loss of 5% difference between active treatment and placebo, the FDA has approved 5 drugs for long term use (greater than 12 weeks) as an adjunct to lifestyle for chronic weight management in individuals with BMI $\geq$ 30.0 kg/m^2 or BMI of 27.0-29.9 kg/m^2 with co-morbidities such as hypertension, diabetes, or dyslipidemia[82,83]. Although nearly half of obese patients meet BMI eligibility criteria for anti-obesity drugs, it is estimated that $\leq$3.5% receive prescriptions for these drugs in the US[84]. Barriers to the initiation or sustained use of obesity medications include lack of insurance coverage, safety concerns, perception of limited efficacy, and reluctance to view obesity as a disease requiring treatment[84–87].

5.9 Efficacy and safety of Contrave® (Naltrexone/Buproprion)

The most recent practice guidelines for medical care of patients with obesity by the American Association of Clinical Endocrinologists (AACE) Board of Directors and the American College of Endocrinology (ACE) Board of Trustees report that the addition of pharmacotherapy produces greater weight loss and weight loss maintenance compared with lifestyle therapy alone and that short term treatment (3-6 months) using weight loss medications has not been demonstrated to

produce longer-term health benefits and cannot be generally recommended based on scientific evidence. In selecting the optimal weight loss medication for each patient, clinicians should consider differences in efficacy, side effects, cautions and warning that characterize medications approved for chronic management of obesity[88]. FDA-approved monotherapy options include phentermine (Adipex-P®), orlistat (Xenical®), lorcaserin (Belviq®) and liraglutide (Saxenda®). However, monotherapies have limited efficacy, in part due to the recruitment of alternate and counter-regulatory pathways.

Consequently, a multi-target approach may provide greater benefit[89]. Combination products approved by the FDA to treat obesity include phentermine/topiramate (Qsymia®) and naltrexone/bupropion (Contrave®). Although the weight loss produced by phentermine/topiramate is superior to naltrexone/bupropion, the safety profile of naltrexone/bupropion has less severe adverse effects. In addition, naltrexone/bupropion is well tolerated, with nausea being the most reported adverse event. Unlike other centrally acting medications, lorcaserin and phentermine/topiramate, naltrexone/bupropion has no abuse potential[90].

Approved by the FDA in September 2014, Contrave is an oral, sustained-release combination of the dopamine and norepinephrine reuptake antagonist bupropion and the opioid antagonist naltrexone. The proposed mechanism of action of the compound involves complementary stimulation of central melanocortin pathways, resulting in increased energy expenditure and reduced appetite[91]. Effects may result from action on areas of the brain involved in the regulation of food intake: the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system).

The safety and efficacy of Contrave were assessed in four randomized, double-blind, placebo-controlled, 56-week Phase III clinical trials in 4536 adult subjects: COR-1, COR-II, COR-BMOD and COR-DM. All four studies demonstrated statistically significant and clinically meaningful weight loss following up to 52 weeks of treatment compared with placebo[92]. Mean total weight loss across studies for Contrave was 6.8% (95% CI, 6.6-7.1%) or 7.3 kg (95% CI, 7.0-7.6 kg) at 1 year, ranging from 5.0% (5.4 kg) in patients with diabetes receiving minimal behavioral intervention to 9.3% (9.7 kg) in those receiving intensive behavioral treatment[93]. In all studies, significantly more participants taking Contrave achieved weight loss of at least 5% at 1 year than placebo, ranging from 44.5% (vs 18.9%) in patients with type 2 diabetes receiving minimal behavioral treatment to 66.4% (vs 42.5%) in patients without diabetes undergoing intensive behavioral treatment.

Additionally, across the four phase 3 studies, treatment with NB32 resulted in statistically significant and clinically meaningful improvements on multiple weight-related cardiometabolic parameters, such as fasting triglyceride levels, fasting HDL, high sensitivity C-reactive protein (CRP), glycemic control in patients with diabetes and fasting glucose/insulin/ Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) in nondiabetics. Furthermore, improved quality of life was associated with weight reduction and was achieved in more subjects treated with Contrave than placebo[94]. Weight loss was associated with significant improvement in the Impact of Weight on Quality of Life questionnaire-Lite (IWQOL-Lite) score compared with

placebo (NB-301, NB-302, and NB-303). There were improvements ($p<0.05$) in Contrave-treated patients compared with placebo-treated in the following subscales:

- Physical function (all four Phase 3 studies);
- Self-esteem (NB-301, NB-302, and NB-303);
- Sexual life (NB-301 and NB-303);
- Public distress (NB-301 and NB-303); and
- Work (NB-301).

Table 2. Phase III trials with Contrave (Naltrexone-Buproprion [NB])

Phase 3 Study	Arms	Study population (BMI ⩾30 or ⩾27 w/comorbidities and ⩽45)	⩾5% Weight loss at 56 weeks	⩾10% Weight loss at 56 weeks
NB-301 COR-I[95]	Placebo (581) NB16 (578) NB32 (583)	Age 18-66 Male 15%, Female 85%	Placebo: 16% NB16: 39% NB32: 48%	Placebo: 7% NB16: 20% NB32: 25%
NB-302 COR-II[96]	Placebo (202) NB32 (591) W/lifestyle change	Age 19-65 Male 10%, Female 90%	Placebo: 42% NB32: 66%	Placebo: 20% NB32: 41%
NB-303 COR-BMOD[97]	Placebo (495) NB32 (1001) ***NB48 (123)	Age 18-65 Male 15%, Female 85%	Placebo: 17% NB32: 50%	Placebo: 6% NB32: 28%
NB-304 COR-T2DM	Placebo (170) NB32 (335)	Age 20-72 Male 44%, Female 56%	Placebo: 19% NB32: 45%	Placebo: 6% NB32: 18%

*NB16 (Naltrexone SR 16mg/day and Buproprion SR 360mg/day)
**NB32 (Naltrexone SR 32 mg/day and Buproprion SR 360mg/day)
*** From week 28-44, nonresponders on NB32 were re-randomized to either continue NB32 or change to Naltrexone SR 48mg/day and Buproprion SR 360mg/day

A recent multicenter, randomized, controlled, open-label trial examined weight-related quality of life, control over eating behavior and sexual function after 26 weeks of treatment with either naltrexone 32 mg with bupropion 360 mg plus a comprehensive lifestyle intervention (NB + CLI, $N = 153$) or usual care (UC, $N = 89$), which included minimal lifestyle intervention. Compared with UC, participants treated with NB + CLI experienced greater improvements in weight-related quality of life, control over eating behavior, and sexual function. NB + CLI and UC participants lost 9.46 and 0.94% respectively of initial body weight at week 26 ($P < 0.0001$). NB + CLI participants had greater improvements in IWQOL-Lite total score than UC participants ($P < 0.0001$). In participants with moderate/severe Binge Eating Scale scores at BL, 91% of NB + CLI and 18% of UC participants experienced categorical improvements. In participants with Arizona Sexual Experiences Scale-defined sexual dysfunction at BL, 58% of NB + CLI and 19% of UC participants no longer met dysfunction criteria at week 26[98].

5.10 Patient Reported Outcomes (PROs)

Being overweight or obese has an important impact on patients' functioning and well-being, particularly physical function[99]. Thus, it will be important to assess the impact of weight loss and POWER-remote on patient-reported outcomes, including pain, fatigue, mental well-being, physical function, endocrine symptoms, sleep, sexual function, and medication adherence. The original POWER study investigated PROs using the MOS SF-12 physical component summary and mental component summary, the EuroQoL-5 dimensions single index and visual analog scale, the Patient Health Questionnaire-8 (PHQ-8) depression symptoms, and the Pittsburgh Sleep Quality Index (PSQI) sleep quality scores at baseline and 6, 12 and 24 months. We will notify the primary oncology provider if the PHQ-8 score is ≥15 (moderately severe or severe depression).

Physical domains were most affected, especially in subjects who lost weight. In another study which involved postmenopausal women undergoing a dietary and/or exercise intervention, weight loss predicted improvement in self-reported physical function, vitality, and mental health[100]. Since physical function has most consistently been found to be improved by weight loss, it will be our primary PRO. Studies in cancer patients suggest a 4-6 point change in score in Physical Function using the National Institute of Health (NIH) Patient-Reported Outcome Measurement Information System (PROMIS) questionnaire to be clinically meaningful[101]. Since minimally important differences is usually estimated by taking half the estimated standard deviation, and in conjunction with the aforementioned studies, we conservatively hypothesize that, compared to baseline, weight loss at 6 months will be associated with an increase of five points in PROMIS, as determined by version 1 short-form to assess physical function. This form was also used in the POWER-remote study.

We will also administer a questionnaire to evaluate modulation in other PROs including: pain, fatigue, mental well-being, sleep, endocrine symptoms, and sexual function. Participants will also complete a drug diary to monitor medication adherence.

5.11 Summary

Treatment of obesity with pharmacotherapy is underutilized in patients whom are unable to achieve weight loss with behavioral interventions. Our results will be used not only to implement a weight loss program for this vulnerable population of breast cancer patients, but also to develop large scale trials assessing breast cancer-related outcomes. Furthermore, we will identify how pharmacotherapy and behavioral weight loss interventions affect biomarkers of obesity and the microbiome, laying groundwork to future trials investigating additional or alternate interventions in those who are not expected to benefit from the program.

6. INCLUSION AND EXCLUSION CRITERIA

This is a single arm phase II study designed to determine the effects of pharmacotherapy and a POWER-remote weight loss intervention implemented as part of routine oncology practice, and the impact of successful weight loss on serum biomarkers of obesity that may be used to design future studies.

6.1 Inclusion criteria

6.1.1 Female, at least 3 months after completion of local therapy (e.g. surgery, radiation), and if applicable, adjuvant chemotherapy

NOTE: Concurrent endocrine therapy or anti-HER2 therapy is permitted. Concurrent enrollment in other interventional or drug clinical trials is at the discretion of the Protocol Chair.

6.1.2 Diagnosed within 15 years with histologically-confirmed ductal carcinoma in situ (DCIS) or stage I-III invasive carcinoma of the breast

6.1.3 Up to date with recommended screening mammography within one year

NOTE: Women who have had a mastectomy (including simple mastectomy, modified radical mastectomy, and radical mastectomy) to treat breast cancer need no further routine screening mammograms on the affected side. If both breasts are removed (a double or bilateral mastectomy), they don't need mammograms at all.

NOTE: Women who have had breast-conserving surgery (e.g., partial mastectomy or lumpectomy) should have a mammogram of the treated breast 6 to 12 months after radiation treatment ends. After that, women should have annual mammograms.

6.1.4 Current BMI ≥ 30 kg/m2 or BMI 27.0-29.9 kg/m2 with hypertension, non-insulin dependent diabetes or hyperlipidemia; and weight ≤ 400 lbs

NOTE: Participants should not have weight loss greater than 5% of body weight in the last 6 months. All weights for determination of eligibility may be determined by self-report of weight if not documented in the medical records. During the study, if any surgical procedures are required, the difference between weight prior to surgery and after surgery will be accounted for and require notification of the Protocol Chair/designee.

6.1.5 Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (Appendix A)

6.1.6 Willingness to change diet, physical activity, track behaviors, engage in weekly and monthly contacts and visit, and take chronic weight loss medication

6.1.8 Able to read and write the English language without assistance and daily access to the e-mail and/or smartphone

NOTE: Participants who are unable to receive email or to complete the online questionnaires for any reason will not be eligible for the study.

6.1.9 Patient is aware of her diagnosis, understands the study regimen, its requirements, risks, and discomforts, and is able and willing to sign an informed consent form.

6.2 Exclusion criteria

6.2.1 Serious/uncontrolled medical condition at the discretion of the Protocol Chair/designee likely to hinder accurate measurement of weight or any condition for which weight loss is contraindicated or would affect adipokine and inflammatory markers (e.g. active malignancy, end stage renal disease on dialysis, cirrhosis, autoimmune disease, adrenal disease, uncontrolled hypertension, seizure disorder, and history of bariatric surgery)

6.2.2 Pregnant or nursing within past 6 months, or plans to become pregnant in the next year

6.2.3 Currently enrolled or planning to enroll in a weight loss program (e.g. Weight Watchers, Jenny Craig, Nutrisystem and Medifast) or to take a chronic weight loss medication.

6.2.4 Diabetes on insulin or sulfonylureas within the past 3 months

6.2.5 Unstable psychiatric disorder or bulimia/anorexia nervosa

6.2.6 Alcohol, nicotine or substance abuse; or undergoing abrupt discontinuation of alcohol, benzodiazepine, barbiturate or anti-epileptic drug

6.2.7 Use of the following medications are excluded:

- Tamoxifen
- MAO inhibitors (must be >14 days from discontinuation)
- Thyroid medication use unless on stable doses for at least the past 3 months
- Buproprion containing products or opiate agonists (must be >14 days from discontinuation)
- Medications that cause weight loss (e.g., lorcaserin, phentermine, orlistat, Qsymia, Contrave) within the past 3 months
- Medications that are likely to cause weight gain or prevent weight loss (e.g., corticosteroids, lithium, olanzapine, risperidone, clozapine, oral contraceptive pills, hormone replacement therapy) within the past 3 months. NOTE: An exception to this is that SSRI's and SNRI's are allowed if participant has been on stable doses for at least 3 months (if discontinued, a washout of 2 weeks from prior SSRI/SNRI use is required).
- Medications that may affect adipokine or inflammatory markers (e.g., metformin, glitazones, steroids, ACE inhibitors, beta blockers and statins) unless on stable doses ≥3 months prior to registration (if discontinued, a washout of 2 weeks from prior use is required). Concurrent NSAIDs are allowed if use is limited to <3 times per week; chronic NSAIDs are permitted on study only if use has been ≥3 times per week for at least 3 months prior to registration and is expected to continue.

NOTE: No medication should be discontinued without guidance of the prescribing provider.

6.3 Inclusion of women and minorities

Women of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. This trial is open to enrollment of women only.

7. STUDY DESIGN AND TREATMENT PLAN

7.1 Recruitment

Patients will be recruited through the breast cancer clinics at Johns Hopkins Medical Institute, including the Sidney Kimmel Comprehensive Cancer Center in Baltimore MD and Green Spring Station in Lutherville-Timonium MD, and Sibley Memorial Hospital in Washington D.C. Participants will also be recruited at LHAAMC in Annapolis MD. Study participants will be prescreened by the Johns Hopkins breast cancer survivor registry from 2015-2019. Patients can also be recruited directly through these clinics. We have previously established our ability to

recruit patients with similar characteristics to a POWER-remote study[4]. Additionally, we are including a recruitment letter from the study Protocol Chair and study oncologist to send to clinic patients that we have been unable to reach by phone. We have also uploaded an online screener that will be administered via REDCAP. The purpose of the screener is to aid in visibility of the study and initial assessment of eligibility. We find that giving interested individuals immediate feedback on their initial eligibility helps them remain interested in the study until the coordinator can call them back. Recruitment may be expanded to include eligible breast cancer survivors in the region with flyers.

7.2 Determination of Eligibility

After eligibility is established by the coordinator during the screening call, the study staff will register participants, assign a study number, and schedule an in-person baseline visit. Participants will not begin protocol-specified treatment until eligibility is confirmed by the study staff at the baseline visit. Participants who sign a consent form, but do not initiate protocol intervention for any reason, will be replaced and will not count towards our accrual goal.

7.3 Visits and Follow up

The study will include a 24-month recruitment period, a 6-month implementation period, which involve 3 in-person visits and at least 16 phone sessions for each participant. We anticipate enrolling 2-4 participants per month. All women will receive the POWER remote behavioral weight loss intervention (BWL) and a behavioral coach. They will all receive lifestyle guidelines (See Appendix B). At week 9, those who lose ≥5%, designated fast responders, will continue with BWL alone (FAST-BWL) while those who lose <5%, designated slow responders, will receive BWL with the addition of Contrave (SLOW-BWL).

Women in SLOW-BWL will initiate Contrave one 8-mg naltrexone/90-mg bupropion tablet per day and increased over 3 weeks to the maintenance dosage of two 8-mg/90-mg tablets twice daily, for a total daily dose of 32mg/360mg. It should be taken by mouth in the morning and in the evening and should not be cut, chewed, or crushed. In clinical trials, Contrave was administered with meals. However, it should not be taken with a high-fat meal because of a resulting significant increase in bupropion and naltrexone systemic exposure. As patients are instructed to follow the DASH (Dietary Approaches to Stop Hypertension) and/or Mediterranean diet, this should not be an issue. Patients will be instructed that ketogenic and low carbohydrate diets would impact the absorption of Contrave.

The behavioral coach will review the weekly weight and new symptoms entry (patient will completed in REDCap survey or via telephone if not done) for months 3-6 for participants in both arms. The REDCap survey (Appendix C) asks patients about any new symptoms and includes examples of those which had a frequency of at least 4% in patients on Contrave in clinical trials. Any new symptoms noted will be directed to the Protocol Chair for further evaluation. If patients on Contrave have significant adverse effects, providers will decrease the dose by 50% and assess tolerability over 1 week. If symptoms are alleviated, patient can

continue at lowered dose. If symptoms persist, dose can be lowered by 50% again. If symptoms are alleviated, patient can continue at lowered dose. However, if symptoms persist, the medication should be discontinued and the patient should continue with BWL alone. Following the prescribing information, Contrave will be discontinued for patients who do not achieve ≥5% and seen in person once a month to assess compliance and potential side effects.

The weight loss intervention is based on the remote-support arm of the POWER trial that was also used by our team in a previous study in breast cancer survivors[3,4]. It involves two main components: an online portion that participants access on their computer or phone and a telephone/teleconferencing portion to help monitor progress and deliver the behavioral intervention. All participants will receive the POWER intervention, which will be remote and last 6 months. Participants will be given a physical activity monitor (Fitbit) that encourages increased activity by measuring steps and process variables, such as heart rate and sleep. Participants will use a web-based platform to access learning materials and log their diet and exercise each day. They will also record their weight once weekly through our survey. As participants monitor their own progress, they will receive telephone/teleconferencing calls on a regular schedule by a weight loss coach to help monitor and guide progress utilizing dietary, physical activity and weight information. All contacts will be phone/teleconferencing based and last about 30 minutes. For all participants, contacts will occur weekly during the first 3 months (a baseline visit followed by 12 phone sessions) and monthly for the remaining 3 months (3 phone sessions). At the conclusion of the study after 6 months of behavioral intervention, participants will have an in-person visit.

7.3.1 Screening (by phone call)

- Informed consent
- History and physical information will be noted from most recent, standard of care assessment included in the medical records. (NOTE: Participants who may be referred from outside the institution may meet with a medical/clinical member of the study staff at baseline; however, a documented H&P by a study team member is not required.)
- Physical measurements (weight and height) as per patient or chart for BMI calculation
- Review of weight loss history
- Collect current medications and medication history
- Smartphone access and/or access to programs online
- Assess willingness to change diet, physical activity, track behaviors, engage in weekly and monthly contacts and visit, and take chronic weight loss medication (yes/no question format)
- Through REDCap, baseline questionnaire should be completed at home ≤2 weeks prior to baseline visit, but may be completed at baseline visit too. As noted in the eligibility, participants that are unable to complete the questionnaires will not be able to

continue/enroll in the study. NOTE: Patients who complete a screening visit, but who are not eligible, will be offered the "Aim for healthy weight" handout (Appendix D).

7.3.2 Baseline Visit

The Baseline Visit is in-person and should ideally occur within 8 weeks of the screening visit; with baseline questionnaires completed ⩽8 weeks prior.

- Written informed consent
- Physical measurements (weight and height) and BMI calculations
- Vital signs (temperature, blood pressure, heart rate, breathing rate, oxygen level)
- Complete medical history and overall general health (performance status)
- If a documented physical exam is not performed within 3 months, this will be performed at or after baseline visit (but before initiation of the behavioral intervention)
- Meet with weight-loss coach
- Receive Fitbit device for monitoring physical activity (participants will wear this on their non-dominant hand for a minimum of 4 of 7 days with 10 hours per day)
- Receive weight scale
- Check heart rate and blood pressure
- Confirm current medications and medication history
- Blood sample (Pregnancy test for < 60 years of age and not taking medication designed to suppress ovarian function. Will advise contraception for these women.)
- Fecal sample
- Orientation to Fitbit website or smartphone platform by coordinator or coach
- Confirm completion of PROs (or complete in clinic, if needed)

IMPORTANT: Eligibility will be confirmed at the baseline visit. Participants with a BMI of ≥27 at the screening visit, but with a BMI of <27 at the baseline visit will not have maintained eligibility and will be excluded at present. In addition, if there is ≥2 kg/m^2 discrepancy between the screening and baseline visits, the Protocol Chair or designee must be consulted to review the discrepancy; this is to determine that the study endpoints will not be affected by fluctuating/changing weight.

7.3.3 Follow-Up Visits

Participants will be asked to attend in-person follow-up visits at 2 months and 6 months.

All Follow-Up Visits are in-person and should ideally occur within 8 weeks of the assessment visit date.

2 months

- Weight and BMI calculations
- Confirm completion of PROs (or complete in clinic, if needed)
- Confirm current medications and medication history
- Blood samples*
- Fecal sample

6 months (End of study)

- Weight and BMI calculations
- Confirm completion of PROs (or complete in clinic, if needed)
- Collect current medications and medication history
- Blood samples*
- Fecal sample

*Blood will be collected while patient is fasting when possible (i.e., 9-12 hours preferred). Will provide patients with juice or bar after labs. Additionally, participants will be asked to be fasting for follow-up visits even in cases when blood samples are not planned to allow for consistency of anthropomorphic data collection.

In participants who discontinue early, the next planned assessments will be completed early whenever possible (e.g., a participant that withdraws at 6 weeks will be asked to complete week 9 assessment; a participant withdraw at 5 months, the end of study assessment). The last visit should be scheduled once the participant has received the full 6 month intervention.

7.4 Measurements

7.4.1 Weight: will be measured at each in-person visit, at approximately the same time of day. The weights are obtained at baseline, week 9 and at the end of study. The ideal weight measurement should be obtained within 7 days of completing the 8 weeks and 6 months behavioral intervention. However, to accommodate participants who may not be able to meet within this window, the weight measurement can be obtained within 14 days of these time points. Weight in light indoor clothes without shoes will be recorded by any trained, certified staff using a high-quality digital scale in any of our Johns Hopkins Medical Institute (JHMI) clinics. Duplicate measurements will be made to ensure accuracy. Weight will be measured in pounds for ease of interpretation by the participants and subsequently converted to kilograms for data analysis. Scales will be calibrated per the Sidney Kimmel Comprehensive Cancer Center's (SKCCC) standards. The engineering department or study staff will perform quarterly calibration checks by using standard weights. The weight at SV will be used to determine eligibility. Measurements will be repeated once, if difference between the two measurements is more than 0.1 kg, measurement will be repeated until difference between two measurements is less than 0.1 kg.

7.4.2 Height: to the nearest 0.1 cm will be measured once at any of our JHMI clinics. The participant stands shoeless on a firm, level surface, with her head in the horizontal (Frankfort) plane. Measurements will be repeated once, if difference between the two measurements is more than 1 cm, measurement will be repeated until difference between two measurements is less than 1 cm.

7.4.3 BMI: will be calculated as the Quetelet index (kg/m^2)

NOTE: All physical measurements should be taken by a member of the study team or an appropriate clinical employee (e.g., clinical associate who regularly collects physical measurements).

7.4.4 Daily steps: are measured by Fitbit. Fitbit devices use a 3-axis Fitbit to understand your motions. An Fitbit is a device that turns movement (acceleration) into digital measurements (data) when attached to the body.

7.4.5 Intensity of physical activity (also known as MVPA, which is moderate to vigorous physical activity): is measured by the Godin Leisure-Time Exercise Questionnaire. Leisure-time physical activity is an important subtype of physical activity (PA) for research and behavior change intervention in oncology context. This is a 3-item self-administered questionnaire with the first three questions seeking information on the number of times one engages in mild, moderate and vigorous PA bouts of at least 15 min duration in a typical week. Examples of PA are provided for each intensity category. Scores derived from the questionnaire include total weekly PA, called a Leisure Score Index (LSI), in which number of bouts at each intensity is multiplied by 3, 5, and 9 metabolic equivalents (METs) and summed. LSI scores can be used for ranking individuals from the lowest to highest PA levels. In addition, the score obtained from MVPA can be used to classify respondents into *active* and *insufficiently active* categories according to published PA guidelines for cancer survivors.

7.5 Questionnaires

7.5.1 Clinical and Demographic Information

The designated research coordinator(s) participating in this project will enter clinical information associated with each participant in the database. Such data could include, but is not limited to: medical record number, age, sex, physical measurements, treatment history, tumor size, tumor grade, tumor receptor status, pathology report, smoking history. Such information will be retrieved from existing clinical databases (e.g., Johns Hopkins Electronic Patient Record) and patient questioning.

Participants will be asked to provide contact information for their other health care providers in case information needed is not contained in the Hopkins clinical databases, or if the participant assumes care outside the institution. In addition, participants may be reached by phone to help with any questions or clarifications, or additional follow-up requirements.

Participants will also be asked about current medications at each visit. This will be documented in the electronic medical record.

7.5.2 Patient Reported Outcomes

We will collect PROs using REDCap, which is already in throughout the institution by several clinical investigations. PROs will include questionnaires regarding physical function, pain, fatigue, mental well-being, endocrine symptoms, sleep, sexual function, and medication adherence, at baseline, 2, and 6 months following initiation of the intervention. Pain, fatigue, mental well-being, sleep, and physical function will be assessed using the NIH PROMIS questionnaire; endocrine symptoms with the FACT-endocrine symptoms, and sexual function

with the MOS-Sexual Function. Medication adherence will be monitored with the institutional drug diary.

Enrolled patients will be given a letter with a username and password for the Fitbit website, and will be oriented on how to use the website; an email address will also be recorded for each participant. Participants will receive e-mail reminders when it is time for them to complete the REDCap questionnaire. They will be encouraged to complete the questionnaire prior to any planned clinic visit; however, they will be informed that a research coordinator can assist them prior to their visit if they prefer to complete the questionnaire at the clinic. Whether patients complete the PRO questionnaire at home or in the clinic, they will access the questionnaires via the internet. At follow-up clinic visits for patients who completed the PRO questionnaires, clinician sub-investigators will have a summary report available to them via REDCap.

Questionnaires will focus on some basic background information and patient reported outcomes, with more detailed survey information as follows. Data from the questionnaires will be available for export into spreadsheets or other tools for analysis.

NOTE: In the event that questionnaires through REDCap are not available, we will use paper-based questionnaires.

The questions that will be included in the REDCap system are included in Appendix E. Score interpretation is in Appendix F. Domains that will be included in REDCap are as follows:

- General health and physical function will be assessed using NIH PROMIS Adult Physical Function Short Form 1[102]. The physical function item bank measures self-reported capability rather than actual performance of physical activities, and generally includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands. A single physical function capability score is obtained from a short form, and has been validated in adults with chronic illnesses.
- Pain will be assessed using the NIH Patient-Reported Outcome Measurement Information System (PROMIS) adult pain interference version 1.0 short form. The pain interference item bank measures the self-reported consequences of pain on various aspects of daily life. This includes the extent to which pain hinders involvement in social, cognitive, emotional, physical, and recreational activities. The short form is comprised of 6 questions which assess pain interference over the previous seven days. Each question has five response options ranging in value from one to five. A total raw score is calculated by summing the values of the response to each question, and then translated into a T-score using a conversion table. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person who has a T-score of 40 is one SD below the U.S. general population mean. Reliability and validity have been previously reported[103].
- Fatigue will be measured using the NIH PROMIS Adult Fatigue Version 1.0 short form. The NIH fatigue question bank evaluates a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and

the impact of fatigue on physical, mental, and social activities. The short form used has 7 questions which assess fatigue over the past seven days. As with all of the PROMIS short forms, each question has five response options ranging in value from one to five. A total raw score is calculated by summing the values of the response to each question, and then translated into a T-score using a conversion table. The T-score rescales the raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. Therefore, a person who has a T-score of 40 is one SD below the U.S. general population mean. Reliability and validity of the fatigue assessment in cancer patients has been reported[104].

- Mental health will be evaluated using the NIH PROMIS Depression and Anxiety questionnaires. The Adult Depression Version 1.0 Short Form is an 8 question survey, and the Adult Anxiety Version 1.0 Short Form is a 7-item survey, for a total of 15 mental health questions. The depression item bank assesses self-reported negative mood (sadness, guilt), views of self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The anxiety item bank measures self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The anxiety and depression scores are calculated individually, in the same way all PROMIS scores are calculated as above.
- Endocrine symptoms will be assessed using the endocrine subscale of the Functional Assessment of Cancer Therapy-Endocrine Symptom questionnaire. The Endocrine Subscale was designed for use with the FACT-B (Functional Assessment of Cancer Therapy for breast cancer patients) but has been tested on its own[105]. It comprises 18 items in which patients indicate how true a statement has been for them over the prior 7 days using a 5-point scale.
- Disturbance in sleep or sleep changes on therapy will be evaluated with the NIH PROMIS Adult Sleep Disturbance Version 1.0 Short Form. The sleep disturbance item bank assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep over the 7 days before questionnaire administration. This includes perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep[106].
- Changes in sexual function will be evaluated using the MOS Sexual Functioning Scale, which consists of four items assessing interest in sex, ability to relax and enjoy sex, arousal, and ability to have an orgasm. Items are rated on a 5-point scale (1=not a problem, 2=little of a problem, 3=somewhat of a problem, 4=very much of a problem, and 5=not applicable). This scale is useful for measuring sexual function in both men and women. It has demonstrated good reliability and construct validity in breast cancer patients[107].
- Medication adherence will be assessed using the institutional drug diary (APPENDIX G).

7.5.3 Nutritional and Physical Activity Assessments

Fruit and vegetable consumption will be measured with National Institutes of Health's Eating at America's Table study[108]. Participants will be asked various questions regarding the frequency and quantity of various food groups in the past month. A total score is calculated by converting

quantity to a standard scale for each food category, multiplying by the frequency, and summing. This questionnaire will be implemented at baseline and follow-up visits (See Appendix E and F).

Participants will wear the Fitbit on their non-dominant hand for seven days and a minimum of four days with ten hours per day of wear time required for analyses. Fitbits have been determined to be reliable and valid measures of physical activity[109]. Established cut-points will be used to determine minutes of moderate to vigorous physical activity[110]. Average daily physical activity will be normalized and reported as minutes per week of moderate to vigorous physical activity. The Fitbits will also capture process variables, such as heart rate and steps.

7.6 BWL intervention

All patients enrolled will receive a 6 month remotely delivered behavioral lifestyle intervention primarily through a web-based platform. For purposes of this study, lifestyle coaches will be supplied by Johns Hopkins. The coaches are trained in both behavioral weight loss principles and motivational interviewing will have access to self-monitoring data through the platform, allowing them to review multiple aspects of adherence to dietary and physical activity behaviors as well as weight loss progress. To tailor the intervention to breast cancer survivors, we have provided the coaches with comprehensive training regarding breast cancer subtypes, types of therapy patients have received and might still be taking (e.g., hormonal, anti-HER2 agents), expected side effects from prior or ongoing therapy (e.g., fatigue, neuropathy, lymphedema, hot flashes), scheduled standard clinic visits and tests, and symptoms disconcerting for a recurrence. Coaches will discuss additional dietary and physical activity recommendations that are standard for breast cancer patients such as moderation of alcohol intake. Patients are provided with modules of recommended exercises per American College of Sports Medicine and American Cancer Society recommendations, particularly in reference to lymphedema prevention[111].

The participants will have access to a web-based platform which provides support for lifestyle counseling in behavioral methods of weight management; a summary of the support and methods will be given at the first/in-person visit with the weight loss coach. Participants in this group will be encouraged to record diet, exercise, and weight on this web-based platform. Web-links to health related websites may also be left by the coach. These participants will receive usual medical care from their providers (i.e., oncologists and primary care physicians). Providers will support and encourage participants to be actively engaged in the lifestyle counseling intervention.

7.6.1 Goals

The goals of this intervention (from months 3-6) are to induce weight loss of 5% or more by adding pharmacotherapy to behavioral weight loss interventions in women whom are unable to achieve 5% weight loss with lifestyle modifications alone.

7.6.2 Description and delivery of the intervention

Participants in this group will receive a behavioral weight loss intervention consisting of:

- Teleconferencing and/or phone calls by coaches (see frequency of contacts below);
- A lifestyle counseling curriculum delivered via the web (hard copies also provided as requested); and

- Online tools for behavioral self-monitoring.

7.6.3 The lifestyle curriculum:

The lifestyle curriculum consists of learning materials which will be provided in a binder and can be provided electronically. The curriculum focuses on self-monitoring, behavioral strategies for modifying eating behavior and increasing physical activity, stimulus control, social support, problem solving, and cognitive restructuring. Goal setting is also a key component of the intervention.

7.6.4 Self-Monitoring

All participants are advised to:

- Record weight at least once each week.
- Record daily: minutes of moderate to vigorous physical activity (MVPA) in bouts of 10 minute bouts or more, and all food and beverages consumed daily using the smartphone application or website.

7.6.5 Participant contact

Participants receive teleconferencing/telephone calls weekly for 3 months and monthly thereafter from lifestyle coaches to encourage completion of learning materials modules, to reinforce key learning points, and to encourage logging and provide feedback on weight, food intake, and exercise tracking. Calls will be each week for months 1-3, once a month for months 4-6. Each call will be approximately 30-45 minutes long. For all participants, coaches will also review and/or inquire about any new symptoms (weekly during months 4-6) and adherence if they are assigned to the arm with the pharmacotherapy. If symptoms are reported, the coach will notify the physician on study and the patient may be contacted by the physician for further evaluation.

7.6.6 Assessment of adherence

Adherence to intervention for participants will be based on completion of coach contacts and modules, and online self-monitoring of weight, food intake, and exercise. Additionally, patients on the SLOW-BWL arm will complete a drug diary log during the one-month long titration (APPENDIX G). Patients will e-mail their logs to the study team for review.

7.6.7 Provider role

At routine medical visits, these participants will be encouraged by their oncologist to actively engage in the intervention. Providers will receive a report that provides a snapshot of their patient's progress and that provides key behavioral recommendations to reinforce.

7.6.8 Description of BWL Intervention

Month 1-3		
Frequency	Weekly	**Entire duration of study** Automated weekly weight entry
Mode	Teleconferencing or phone calls	

Month 4-6		Entry of diet and exercise
Frequency	Monthly	
Mode	Teleconferencing or phone calls	

The SLOW-BWL group will have the addition of Contrave to BWL from Month 4-6

*From months 4-6, for any patients in either arms who are struggling with weight loss (i.e. motivation, behavioral concerns, weight regain etc.), an additional 2 "booster" visits can be scheduled through teleconferencing sessions.

7.6.9 Weight Goals and Behavioral Recommendations

Remote-Support Weight Loss Intervention	
Weight Loss Goal	Minimum 5% weight loss, individually tailored
Behavioral Recommendations	
Total Calorie Intake	Active weight loss 1200 kcal/d if ≤ 170 lbs 1500 kcal/d if > 170 lbs and < 200 lbs 1800 kcal/d if > 200 lbs and < 270 lbs 2200 kcal/d if > 270 lbs Maintaining weight loss 1500 – 1900 kcal/d
Dietary Pattern	Option 1: DASH diet 7-12 servings of fruits/vegetables 2-3 servings of low fat dairy Low sodium ≤ 25% of calories from fat Option 2: Mediterranean diet Daily consumption of vegetables, fruits, whole grains and healthy fats Weekly intake of fish, poultry, beans and eggs Moderate portions of dairy products Limited intake of red meat and alcohol
Physical Activity	Build to ≥ 180 minutes/week of moderate intensity physical activity in bouts ≥ 10 minutes in length
Self-Monitoring Recommendations	
Weight	Weekly
Calorie counting	Daily
Physical activity	Daily
Mode	Online behavioral tracking of above behaviors

7.7. Concomitant and Supportive Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the medical records. Any

changes in medications during the study must be clearly documented in the study records. The administration of any other therapies intended to treat the breast cancer, with the exception of trastuzumab (Herceptin®) and endocrine treatment (i.e., aromatase inhibitor) is NOT permitted. As noted, changes in endocrine treatment during study participation should be avoided. The initiation of or changes to any ongoing medications listed in Section 6.2.4 should also be avoided, if possible.

7.8 Discontinuation and withdrawal of subjects

Participants who discontinue the study early will be asked to complete the next planned assessment at the time of discontinuation, if feasible and acceptable to the patient. All reasons for discontinuation of therapy should be documented clearly in the medical record.

7.11 Discontinuation of intervention

The intervention will continue for the planned 6 months except in patients who fulfill one or more of the following criteria:

- Diagnosis of new or recurrent intraductal or invasive breast cancer while on therapy where a change in treatment is planned.
- Intercurrent illness or change in the patient's condition that renders the patient unacceptable for further treatment in the judgment of the principal investigator (PI).
- Pregnancy
- Lack of compliance with treatment assignment.
- Patient request to discontinue protocol.

7.12 Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent.
- Subject needs treatment not allowed in the study.
- Study is lost to follow-up.
- Study is canceled for any reason.

7.13 Additional Information

Participants who complete the study will be gifted the Fitbit and weight scale in appreciation of their time at the final study visit. Participants will also be offered parking vouchers at the end of each study visit, if applicable. Additionally, for patients who have completed the study and would like to continue weight management care within Johns Hopkins, the team will provide referrals to the Digestive Weight Loss Center (at Green Spring Station, Sibley Memorial Hospital or Johns Hopkins Hospital). This information will be included in the informed consent document.

8. STUDY CALENDAR

Procedure	Screening call for eligibility	Baseline Visit ##	Follow-Up Visits ##		
			Week 9		Month 6
Clinical & Physical Assessments:					
Consent		X			
Questionnaires		X			
History	X				
Physical exam		X#			
Current medications	X	X			
Performance status		X			
Weight Loss History	X				
Vitals		X	X		X
Up to date screening mammography within one year	X				
BMI Calculation	X*	X	X		X
Anthropomorphic Measurements:					
Height	X*	X			
Weight	X*	X	X		X
Research Correlates:					
Fecal sample		X	X		X
Serum pregnancy test (if age <60)		X			
Lipid panel, Hba1c		X	X		X
Purple research tube		X			
Red/gray research tube		X	X		X
Research Intervention:					
Patient Reported Outcomes		X	X		X
Provide Fitbit**		X			
Coaching (BWL intervention)***		X	X		X
Provide weight scale		X			

*If greater than 3 months since last documented height and weight in electronic health record, will use patient reported most recent height and weight to determine eligibility based on BMI. However, BMI measured at baseline will serve as first data point.

**Participants will wear the Fitbit on your non-dominant hand for 7 days and a minimum of 4 days with 10 hours per day of wear time.

***Participants will communicate with their coach by phone. The coach will reach out to the participants at the baseline visit, and will provide weekly calls and emails the first 3 months. The last 3 months, participants will receive monthly calls and emails.

[#] Physical exam: may be performed and documented up to 3 months prior to baseline visit by a co-investigator or provider within the institution. Or physical exam may be performed at or after baseline visit (but before initiation of the behavioral intervention)

Baseline visits should occur within 8 weeks of screening visit. Follow up visits should occur within 8 weeks of assessment date.

NOTE: Additional standard of care tests may be performed at the discretion of the treating investigator as clinically indicated. The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the PI/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study or subject safety are affected.

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

9. CORRELATIVE STUDIES

9.1 Blood Samples

9.1.1 Collection

Approximately 15 mL (3 tubes) of blood will be collected at each time point (a standard 5 mL tube for lipid panel and Hba1c, one 10 mL red/gray research tubes). An additional 8 mL will be collected at the initial blood draw to include a 5mL red top tube for pregnancy test and 3 mL purple EDTA tube are collected for research once only. If blood samples are missed or unable to be obtained at any time point, this will not be considered a deviation and will not affect participant enrollment or continuation on the study. We will test glucose, insulin, lipid profiles (total cholesterol, HDL, LDL, and triglycerides), leptin and adiponectin, several fasting biomarkers, and various genotypes (e.g. MnSOD). The samples will be processed by either the central lab or local laboratories (See Lab Manual). In the event that blood cannot be collected, the subject may still take part in the other portions of the study.

	Baseline	2 months	6 months
Standard 5 mL gold tube (lipid panel, Hba1c)	X	X	X

Pregnancy test 5 mL red tube (if indicated)	X		
Purple 3 mL tube	X		
Red/gray 10 mL tube	X	X	X

9.1.2 Analysis

Biomarkers will be processed and batch analyzed whenever possible to reduce within- and between-batch variability at a designated facility (e.g., the Johns Hopkins Medical laboratories Services).

9.2 Fecal Samples

Participants will provide fecal samples three times during the study and will be provided with the fecal occult blood test (FOBT) to collect the sample at home after a bowel movement. They will ship the fecal sample to the lab of Dr. Sharma at Johns Hopkins University. Upon arrival at the lab, the specimens will be stored at −80°C and will be processed for microbiome analyses. Analysis targeting the V4 region of the 16S rRNA gene will be performed using an Illumina MiSeq and analyses of the microbiome samples will be performed using the Quantitative Insight into Microbial Ecology (QIIME) suite, V.1.7 and a QIIME wrapper (QWRAP).

9.3 Leftover Samples

Any leftover study blood and stool samples will be stored for future research studies, including predictive biomarker studies. These samples may be released for use in future studies after approval by the Protocol Chair and other regulatory bodies, as appropriate.

9.4 Additional information

The correlative sample collection schedules outlined are based on an ideal subject. The sample schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc).

10. ADVERSE EVENTS

10.1 General

This study will use the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/reporting/ctc.html. Information about all related adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

It should be noted that only those adverse events believed to be related to the weight loss intervention will be collected and tabulated during the course of the study. The side effects with

the weight loss intervention we might encounter include anxiety and frustration. While this program is not designed to cause radical weight loss, in the unlikely event this were to occur radical weight loss can cause several medical implications including dehydration, malnutrition, electrolyte disturbances, headaches, nausea, and tachycardia. Blood samples for research correlated will require intravenous access which may include discomfort, bruising and, rarely, infection, syncope, or significant bleeding; these will be collected at planned standard of care testing, whenever possible.

10.2 Potential Risk from Intervention

The following sections describe potential risks associated with the remote-support weight loss intervention along with procedures to minimize risk.

10.2.1 Physical Activity

During the screening process, we will exclude persons with uncontrolled medical illnesses for which physical activity would be contraindicated.

In order to protect the participants' safety, we will continuously reinforce our recommendation to engage in moderate-intensity physical activity. We will also recommend a safety evaluation by their Primary Care Physician (PCP) for those participants who wish to progress to vigorous physical activity. Still, it is important to acknowledge the participant autonomy. We can recommend that participants follow safety advice but cannot force them to do so.

10.2.2 Nutrient Intake

Calorie restriction can theoretically lead to inadequate nutrition or excessive, rapid weight loss (>10% weight loss within 4 weeks or a total weight loss of >25%). If a participant loses >10% weight within 4 weeks, the team will review the patient's food diary to ensure that they are not over restricting their calories (e.g., <1000 daily). If people achieve more than a 25% weight loss, then the team will evaluate for cancer (recurrence in our population), eating disorders, and hyperthyroidism. To minimize these risks, participants are encouraged to eat a variety of foods from all food groups and to maintain an adequate calorie level. If nutritional deficiency is suspected and unresponsive to advice from the interventionist, the intervention will be suspended and the participant will be referred to her PCP. Participants will be advised that marked and sustained caloric restriction can have serious health risks, e.g., malnutrition.

10.2.3 Hypoglycemia

For patients who may be susceptible to hypoglycemia due to use of anti-diabetic medications, weight loss interventions have the potential to increase the risk of hypoglycemia, especially during the time when diet and/or physical activity interventions are implemented. For this reason we will exclude patients who take insulin or sulfonylureas. We will allow patients to enroll if their diabetes is controlled on metformin. If participants have a drop in HbA1c to <6.5 or if they require a change in diabetic medications during this study, they will be overseen by the Protocol Chair and/or co-investigator and the PCP will be notified of these changes.

10.2.4 Symptomatic Hypotension

For patients who may be susceptible to hypotension because they are using medications that lower blood pressure, weight-loss interventions have the potential to increase the risk of hypotension. Participants are educated about symptoms of hypotension and urged to contact the research nurse or PCP if they have symptoms suggestive of hypotension. In addition, staff contact will notify the Protocol Chairof participants who develop symptomatic hypotension while on anti-hypertensive medications. Changes in blood pressure regimen may be performed by the Protocol Chair and/or co-investigators and the participant's PCP will be notified.

10.2.5 Cardiovascular Events

All participants with cardiovascular disease (CVD) require approval from their PCP and Protocol Chair prior to enrolling. If this medical condition is not felt to be stable, patients will be excluded from this study. In addition, participants are educated about CVD symptoms and urged to contact their PCP if they have a change in their CVD symptoms. Overall CVD management remains under the control of the participant's PCP.

10.2.6 Symptoms Related to Contrave

The pharmacotherapy could lead to adverse effects: nausea (NB32 29%, NB16 27%). Headache (NB32 13%, NB16 27%), constipation (NB32 15%, NB16 15%), dizziness (NB32 9%, NB16 7%), insomnia (NB32 7%, NB16 6%), vomiting (NB32 9%, NB16 6%), and dry mouth (NB32 7%, NB16 7%)[95]. Adverse events were most frequently gastrointestinal in nature. The most common of these, nausea was generally mild to moderate in intensity, transient, and did not result in discontinuation for most participants who reported it. Nausea was typically first reported during dose escalation in the experimental groups; the rate of onset seemed to plateau shortly after reaching full dose and then was similar to the rate reported in the placebo group. The most frequent adverse events leading to discontinuation before week 26 included nausea (10.5%); anxiety (3.3%); and headache, hypertension, insomnia and palpitations (1.3% each)[98]. While attrition across all phase III studies of Contrave ranged from 42% to 50%, only 24% of those taking Contrave withdrew due to adverse events (vs 12% taking placebo)[93].

Participants will be educated about the side effect profile and urged to contact the research nurse if they have symptoms. Depending on the severity of the side effect, the dosage may be decreased or discontinued entirely. Patients whom are discontinued on the pharmacotherapy will continue the study with BWL alone. Changes in overall management of hypertension remain under the control of the PI.

10.2.6 Survey fatigue

Minimal risks associated with completing the questionnaires include subject fatigue and the possibility of minor psychological distress. Participants are instructed that they may refuse to answer any questions.

10.3 Definitions

- Adverse event (AE): Any undesirable sign, symptom or medical condition occurring after starting therapy even if the event is not considered to be related to the study. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g.,

tachycardia) or the abnormal results of an investigation (e.g., laboratory findings, biopsies).

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form will be recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

- Serious adverse event or reaction: Any untoward medical occurrence secondary to therapy that: results in death, is immediately life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, or is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.
  A hospitalization planned before the start of the study agent(s) and/or for a preexisting condition that has not worsened does not constitute a serious adverse event (e.g., elective hospitalization for breast reconstruction of the ipsilateral breast). A hospitalization for a social reason in the absence of an adverse event also does not meet the criteria for a serious adverse event.
- Unexpected adverse event: An adverse event, which varies in nature, intensity or frequency from information on the investigational intervention provided in the Investigator's Brochure, package insert or safety reports. Any adverse event that is not included in the informed consent is considered "unexpected".
- Expected (known) adverse event: An adverse event, which has been reported in the Investigator's Brochure. An adverse event is considered "expected", only if it is included in the informed consent document as a risk.

10.4 Relationship

The relationship of all adverse events and serious adverse events to study medication will be assessed by an investigator and assigned as follows:

- Definitely: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, for which no alternative cause is present.
- Probably: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, but for which a potential alternative cause may be present.

- Possibly: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, but a potential alternative cause does not exist.
- Unlikely: An adverse event which does not have a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational drug/agent.
- Unrelated: An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational drug/agent. In general, there is no timely relationship to the administration of the investigational drug/agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause

10.5 Reporting Procedures

10.5.1 General

All adverse events will be captured on the appropriate study-specific case report forms (CRFs) through CRMS and REDCap. The Coordinating Center may also periodically request that de-identified AE logs and deviation logs be submitted via encrypted email, such as for annual continuing review.

10.5.2 Serious Adverse Events

All serious adverse events, regardless of causality to intervention, will be reported to the PI.

10.5.3 Institutional Review Board (IRB)

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires

modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

10.5.4 Reporting to Coordinating Center

All prompt reporting to the protocol chair must be submitted via encrypted email, preferably with subject line starting with "URGENT: J1999", and must be sent to ALL of the following email addresses:

- jsheng7jhmi.edu
- HopkinsBreastTrials@jhmi.edu
- ftoo1@jhmi.edu

NOTE: Entering data in the study database or eCRFs (e.g., REDCap) is NOT an acceptable means of reporting to the sponsor. Likewise, reporting to the sponsor via email does not replace the need to enter data in the study database as applicable.

Do not include patient name, medical record number, or other unneeded patient identifiers in reports to the protocol chair.

11. DATA AND SAFETY MONITORING

11.1 Data management

Participant information relevant to the study will be recorded on a paper case report forms customized for this study. Only the PI and authorized staff, according to the list of Authorized Study Personnel are entitled to make entries on these forms. Case report forms will identify patients by initials and number only. Personal patient data will be kept confidential. The PI will keep in his/her file a Patient Identification and Enrollment List. Data generated from the case report forms will be transferred to a study database on REDCap (https://www.jhubc.org/REDCap/) - a secure, web-based application for building and managing online surveys and databases. All information obtained during the study will be regarded as confidential. All study data will be reviewed for completeness and accuracy by the coordinating center. The study data will also be periodically reviewed by the SKCCC Clinical Research Office (CRO).

11.2 Meetings

Scheduled meetings will take place as needed with the medical oncology co-investigators and study personnel. In addition, separate meetings will be scheduled and include the protocol PI, study coordinator(s), data manager(s), collaborators, and biostatistician involved with the conduct of the protocol. During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to

expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

11.3 Monitoring

This is a project which does not include an investigational drug, agent, or device. Thus, the monitoring will be done by the project personnel.

The project may be periodically monitored by the SKCCC Clinical Research Review Committee (responsible for scientific oversight of studies) and the SKCCC CRO.

This is a non-therapeutic interventional trial, which is DSMP low risk study under the SKCCC Data Safety Monitoring Plan version 6.0 (dated 2/21/2019). The CRO QA Group will perform a regulatory and limited subject review during the last year of study with random selection of 10% of all subjects. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee.

11.4 Data Safety Monitoring Board

In the event of any questions or matters related to the disclosure policy in publications or in the informed consent document, an External Advisory Committee will be assembled, as needed, and will be comprised of members who are not affiliated with 1) the Department of Medicine; 2) neither the adaptive weight loss study and/or 3) Fitbit.

12. ADMINISTRATIVE PROCEDURES

12.1 Registration Procedures

For potential patients of this study, study teams are asked to inform the Coordinating Center of the date and time that the patient will need to be registered.

For non-Hopkins participating sites, all registration materials should be redacted/de-identified and received at least 24 hours prior to when eligibility confirmation is needed (submissions after 4pm will be considered received the next business day). Submit via encrypted email to the following:

- Protocol Chair (Dr. Jennifer Sheng): jsheng7@jhmi.edu
- JH Coordinating Center (HBT and Faith Too):
    - HopkinsBreastTrials@jhmi.edu
    - ftoo1@jhmi.edu

Subjects will be registered with the study coordinator at the coordinating center (Johns Hopkins) once an informed consent form is signed. After eligibility is established, the Coordinating Center study coordinator will assign a study number. Subjects will not begin protocol-specified treatment until eligibility is confirmed and the patient is assigned a study number.

Upon review of the registration documents, the Coordinating Center at Johns Hopkins will confirm successful registration by return encrypted email to the local study team/designee.

12.2 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation.

Amendments will be distributed by the coordinating center of the lead institution (Johns Hopkins) to all affiliate sites upon approval by the Johns Hopkins IRB. Requests or questions from sub-sites regarding study documents (such as to obtain a missing document) can be submitted through the coordinating center

12.3 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the project, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the project is voluntary and that he/she may withdraw from the project at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The subject should read and consider the statement before signing and dating it, and will be given a copy of the document. No subject will enter the project before his/her informed consent has been obtained.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written informed consent document will include a subject authorization to release medical information to the project sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the project, including subjects' medical history. Our protocol does not contain any proprietary (nonpublic) information from an industry sponsor.

12.4 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.5 Regulatory Authorities

Information regarding study conduct and progress will be reported to the JHM IRB per the current institutional standards. This trial does not use a medication, device, or product which requires FDA oversight and no reporting is required with regards to the clinical trial outlined at

this time. The protocol will be submitted to the NCI for its registration with Clinical Trials Registration Program (CTRP).

12.5.1 JHM Single IRB

Johns Hopkins Medicine is serving as the single IRB for this study. It is the preference of Johns Hopkins Medicine IRB to use the SMART IRB reliance agreement as the basis of reliance. The SMART IRB master reliance agreement was created in 2016 to harmonize and streamline the IRB review process for multisite studies. It enables reliance on a study-by-study basis, clearly defines roles and responsibilities of relying institutions and reviewing IRBs, and eliminates the need to sign reliance agreements for each study [e.g., a non-SMART IRB agreement]. 900+ institutions have already signed onto this agreement and are actively using it as the basis of reliance for multisite projects. Sites that will rely on JHM IRB are still responsible for conducting a local context review prior to the start of research at their site and for following any local and institutionally required policies as it applies to research at their site [e.g., reporting of unanticipated problems].

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a prospective, non-randomized clinical trial assessing the effects of the addition of pharmacotherapy to a behavioral weight loss intervention in overweight/obese breast cancer patients on an AI who are unable to attain at least 5% weight loss after 8 weeks of lifestyle intervention alone.

All enrolled patients will participate in a 6-month BWL program. At week 9, patients who achieve ≥5% weight loss from baseline will continue with BWL (FAST-BWL). Those failing to achieve a minimum of 5% weight loss will receive Contrave in addition to BWL (SLOW-BWL). After a 4-week titration of Contrave, SLOW-BWL will have their drug adherence logs and any new symptoms reviewed by the Protocol Chair and/or co-investigators. The participants will be prescribed the constant dose for 3 months until the end of study (drug will be shipped to patient's home).

The primary endpoint of this study is the proportion of SLOW-BWL patients who achieve at least 5% weight loss of their enrollment baseline weight at 6 months with the addition of Contrave to BWL. We anticipate 55% of 55 subjects enrolled will be in the SLOW-BWL group, resulting in a sample size of approximately 30 SLOW-BWL women and 25 FAST-BWL women.

The secondary endpoints include baseline, 2 and 6 months values in all participants for the following: cardiometabolic biomarkers (fasting glucose, fasting lipids, fasting insulin, adiponectin and leptin levels), genotypes, microbiome composition, body composition, patient-reported outcomes (PROs), and physical activities.

Simon's two-stage minimax design will be used for the SLOW-BWL group. The null hypothesis that the true rate of attaining ⩾5% weight loss is 10.9%, which is chosen based on the rate of

women attaining ≥5% weight loss in the self-directed arm in the POWER-remote study.[4] In the first stage, 15 SLOW-BWL women will be accrued. If there is 1 or fewer woman out of the 15 women who attain ⩾5% weight loss of their baseline weight, the study will be stopped. Otherwise, 15 additional SLOW-BWL women will be accrued for a total of 30 SLOW-BWL patients. The study does not plan to hold enrollment or treatment for the interim analysis. The null hypothesis will be rejected if 7 or more women are observed in the 30 patients who attain ⩾5% weight loss. This design yields a power of 80% at type I error rate of 5% when the true rate of attaining ⩾5% weight loss of the baseline weight for the SLOW-BWL women is 29%, a clinical meaningful rate for the SLOW-BWL women group.

Our results will inform us of how to better treat obesity in this vulnerable group of breast cancer patients. It may allow us to develop larger adaptive trials to assess long term breast cancer and non-cancer outcomes of behavioral interventions that incorporate pharmacotherapy. Additionally, our results may shed light on other modulators or obesity, such as biomarkers and the microbiome, laying foundation to future trials investigating additional interventions in breast cancer survivors who struggle with weight loss.

13.2 Analysis Plans

Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy measurements at 2 and 6 months, and safety measurements throughout the study.

For the primary analysis, the study will be considered successful if there are 7 or more SLOW-BWL patients who could achieve more than 5% weight loss compared to their baseline weight, which implies that the success rate regarding to >=5% weight loss will be significantly higher than 10.9%.

Univariate analysis will be conducted to compare outcomes at different time points including baseline, 2 months and 6 months, and to compare outcomes from different groups including SLOW-BWL patients who attain ≥5% weight loss or <5% weight loss of their enrollment baseline weight at 6 months and FASE-BWL patients. Wilcoxon rank sum and Wilcoxon sign rank tests will be conducted when appropriate. Student's t-test will also be performed when the outcomes are normally distributed after necessary data transformation. Moreover, mixed effect regression analysis will be conducted to evaluate the longitudinal trend in the outcomes at different time points.

Furthermore, multivariate logistic regression analysis will be conducted to evaluate the effect of the baseline characteristics on attaining ≥5% weight loss of the baseline weight at 2 months among FAST- and SLOW-BWL patients, and to evaluate the effect of the baseline characteristics and the weight loss at 2 months on attaining ≥5% weight loss of the baseline weight at 6 months for SLOW-BWL patients.

The primary analysis dataset will be based on the intent-to-treat population. Analysis based on the per-protocol population will also be conducted as exploratory analysis. Missing data will be handled by multiple imputation and sensitivity analysis.

13.3 Early Stopping

Following the Simon's two-stage design, the study will be stopped early for futility if there is 1 or fewer woman who attain ⩾5% weight loss in the first 15 SLOW-BWL women.

13.4 Analysis Populations

Intent to treat (ITT) population:

The ITT population comprises all SLOW-BWL women who receive any Contrave. Women who discontinue or are lost to follow-up prior to evaluation of the primary endpoint will be considered to have not achieved ≥5% weight loss, and will not be replaced.

Safety population:

The safety population comprises patients who enroll in the study and participate in BWL alone or BWL + Contrave.

Per-protocol population:

The per-protocol population comprises all patients who were compliant with the study.

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APPENDICES

A: ECOG Performance Scale

B: Lifestyle Guidelines Handout

C: Symptom checklist

D: Aim for a Healthy Weight Brochure

E: PRO Questionnaire

F: Score Interpretation

G: Drug diary

APPENDIX A: ECOG Performance Status Scale

Score	Definition
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed less than 50% of day
3	Symptomatic, in bed more than 50% of day, but not bedridden
4	Bedridden

APPENDIX B: Lifestyle Guidelines Handout
Goal: Lose 5% or more of your body weight at 2 months and maintain weight loss

1. Keep calories in moderation*

To lose weight, if you currently weigh:

Less than 170 pounds: Consume approximately 1200 calories each day
171-220 pounds: Consume approximately 1500 calories each day
221-270 pounds: Consume approximately 1800 calories each day
More than 270 pounds: Consume approximately 2200 calories each day

*Calorie levels: There is not one specific number that's right for you all the time. Your calorie need may change depending on exercise, lifestyle and where you are in the weight loss process.

2. Exercise regularly

We recommend moderate intensity aerobic exercise 30 – 60 minutes for 5 – 7 days per week in bouts of at least 10 minutes. Start with 60 minutes per week and gradually increase each week so that at Week 21, you are reaching 180 minutes of aerobic exercise per week.

3. Weigh yourself weekly when trying to lose weight and daily to maintain weight loss.

When you do weigh yourself, enter it into the website. Be sure to do this at least once per week.

4. Keep track of your eating and exercise.

Daily track your food, beverage and exercise type and minutes and Log on to the Fitbit website at least once per week and enter all your tracking information. We understand that it may be challenging to track your food over a 24 hours period every day of the week. We encourage you to log 24 hours of what you eat at least 4 of 7 days of the week.

Fitbit device for monitoring physical activity (wear this on your non-dominant hand for a minimum of 4 of 7 days with 10 hours per day)

5. Be an active study participant

Attend data collection visits and complete surveys at week 8 and 6 month follow-up. Keep all appointments with your Coach and complete Learning Focuses before calls.

Other recommended guidelines

Follow one of two eating styles:

1) The DASH diet
   - Eat 7-12 servings of fruits and vegetables every day
   - Eat 2-3 servings of low-fat dairy foods every day
   - Eat 25% or less of your total calories from fat
2) The Mediterranean diet

3)

- Daily consumption of vegetables, fruits, whole grains and healthy fats
- Weekly intake of fish, poultry, beans and eggs
- Moderate portions of dairy products
- Limited intake of red meat and alcohol

Eat a low-sodium diet

- Eat 2400 mg or less of sodium each day

Limit alcohol intake

- Women: Drink no more than one drink per day
- Men: Drink no more than two drinks per day

1 drink=12 ounces beer, 5 ounces wine, or 1 jigger (1 ½ ounce) of 80-proof liquor

APPENDIX C: Weekly weight and symptom survey

During the behavioral intervention, coaches call patients weekly the first 3 months, followed by monthly for months 4-6. Patients will receive a REDCap survey on a weekly basis with the following question:

1) What is your weight this week? _____

**If patients have not completed this survey before the call with the coach, the coach may enter the data that is conveyed verbally.*

During months 3-6, ALL study participants will continue with weekly survey, in addition to a question about any new symptoms:

2) During the past 7 days, have you experienced any new symptoms (such as abdominal pain, anxiety, constipation, diarrhea, dizziness, dry mouth, fatigue, gastroenteritis, headache, hot flush, insomnia, nausea, tremor, vomiting etc.)?

   _____

**If patients have not completed this survey before the call with the coach, the coach may enter the data that is conveyed verbally.*

***The coordinator will review all new symptom entries in the REDCap survey on a weekly basis, and new symptoms will be reported to the PI for further evaluation.*

APPENDIX D: Aim for a Healthy Weight Brochure

Participants who are not eligible for the study at the screening visit will be provided the NHLBI publication "Aim for A Healthy Weight."

The publication is publically available and will be downloaded from the National Institutes of Health's website to be given to study participants:

http://www.nhlbi.nih.gov/health/public/heart/obesity/aim_hwt.pdf

APPENDIX E: PRO Questionnaire

The following represents the questions to be asked in the REDCap survey.

CLINICAL AND DEMOGRAPHIC INFROMATION

I. Demographics:

a. What is your date of birth?
b. What is your age?
c. Are you Hispanic or Latino?
    i. Yes
    ii. No
d. What is your race?
    i. White/Caucasian
    ii. Black or African American
    iii. Asian
    iv. Native Hawaiian or Pacific Islander
    v. American Indian or Alaska Native
    vi. Other, _____

II. Past Medical/social/family history

1. Have you had a menstrual period in the past 12 months?
    a. Yes
    b. No

2. If you have not had a menstrual period in the last 12 months, at what age did you stop having periods? (free text)

3. During the past year how many alcoholic beverages did you have?
    a. Never or less than 1 per month
    b. 1-3 per month
    c. 1 per week
    d. 2-4 per week
    e. 5-6 per week
    f. 1 per day
    g. 2-3 per day
    h. 4-5 per day

i. More than 5 per day

4. Have you ever smoked?
    a. Yes
    b. No

5. If you have ever smoked, please indicate how many cigarettes you smoked when you were smoking:
    a. Never smoked
    b. Less than one-half pack per day
    c. One-half to one pack per day
    d. Two packs per day
    e. Three packs per day
    f. More than three packs per day

6. If you have ever smoked, please indicate how many years you smoked:
    a. One year
    b. 2-5 years
    c. 6-10 years
    d. 11-15 years
    e. 16-20 years
    f. 21-25 years
    g. 26-30 years
    h. 31-35 years
    i. >35 years

III. Medications

1. Which of the following medications are you taking? (Select all that apply)

    a. Tamoxifen
    b. Raloxifene (Evista)
    c. Anastrozole (Arimidex)
    a. Letrozole (Femara)
    b. Exemestane (Aromasin)
    c. Goserelin (Zoladex)
    d. Leuprolide (Lupron)

IV. Patient Reported Outcomes (PROs) – Sleep

In the past month…

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

g) Feel too hot

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

h) Had bad dreams

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

i) Have pain

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

7. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

8. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the	Less than	Once or twice	Three or more
past month_____	once a week_____	a week_____	times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all	_____
Only a very slight problem	_____
Somewhat of a problem	_____
A very big problem	_____

V. Patient Reported Outcomes (PROs) – Physical Function

1. Does your health now limit you in doing vigorous activities such as running, lifting heavy objects, participating in strenuous sports?
    a. Not at all
    b. Very little
    c. Somewhat
    d. Quite a lot
    e. Cannot do

2. Does your health now limit you in walking more than a mile?
    a. Not at all
    b. Very little
    c. Somewhat
    d. Quite a lot
    e. Cannot do

3. Does your health now limit you in climbing one flight of stairs?
    a. Not at all
    b. Very little
    c. Somewhat
    d. Quite a lot
    e. Cannot do

4. Does your health now limit you in lifting or carrying groceries?
    a. Not at all
    b. Very little
    c. Somewhat
    d. Quite a lot

e. Cannot do

5. Does your health now limit you in bending, kneeling or stooping?
    a. Not at all
    b. Very little
    c. Somewhat
    d. Quite a lot
    e. Cannot do

6. Are you able to do chores such as vacuuming or yard work?
    a. Without any difficulty
    b. With a little difficulty
    c. With some difficulty
    d. With much difficulty
    e. Unable to do

7. Are you able to dress yourself, including tying shoelaces and doing buttons?
    a. Without any difficulty
    b. With a little difficulty
    c. With some difficulty
    d. With much difficulty
    e. Unable to do

8. Are you able to shampoo your hair?
    a. Without any difficulty
    b. With a little difficulty
    c. With some difficulty
    d. With much difficulty
    e. Unable to do
9. Are you able to wash and dry your body?
    a. Without any difficulty
    b. With a little difficulty
    c. With some difficulty
    d. With much difficulty
    e. Unable to do

10. Are you able to get on and off the toilet?
    a. Without any difficulty
    b. With a little difficulty
    c. With some difficulty
    d. With much difficulty
    e. Unable to do

VI. Patient Reported Outcomes (PROs) - Anxiety

In the past 7 days……

1. I felt fearful
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

2. I felt anxious
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

3. I felt worried
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

4. I found it hard to focus on anything other than my anxiety
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

5. I felt nervous
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

6. I felt uneasy
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

7. I felt tense
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

VII. Patient Reported Outcomes (PROs) - Depression

In the past 7 days….

1. I felt worthless
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

2. I felt that I had nothing to look forward to
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

3. I felt helpless
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always
4. I felt sad
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

5. I felt like a failure
    a. Never
    b. Rarely
    c. Sometimes
    d. Often

e. Always

6. I felt depressed
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

7. I felt unhappy
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

8. I felt hopeless
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

VIII. Patient Reported Outcomes (PROs) - Pain

In the past 7 days…..

1. How much did pain interfere with your enjoyment of life?
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much
2. How much did pain interfere with your ability to concentrate?
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

3. How much did pain interfere with your day to day activities?
    a. Not at all
    b. A little bit
    c. Somewhat

d. Quite a bit
e. Very much

4. How much did pain interfere with your enjoyment of recreational activities?
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

5. How much did pain interfere with your doing tasks away from home (eg. getting groceries, running errands)?
    a. Not at all
    b. A little bit
    c. Somewhat
    d. Quite a bit
    e. Very much

6. How often did pain keep you from socializing with others?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

IX. Patient Reported Outcomes (PROs) - Fatigue

In the past 7 days…..

1. How often did you feel tired?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always
2. How often did you experience extreme exhaustion?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

3. How often did you run out of energy?
    a. Never

b. Rarely
c. Sometimes
d. Often
e. Always

4. How often did your fatigue limit you at work (include work at home)?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

5. How often were you too tired to think clearly?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

6. How often were you too tired to take a bath or shower?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

7. How often did you have enough energy to exercise strenuously?
    a. Never
    b. Rarely
    c. Sometimes
    d. Often
    e. Always

X. Patient Reported Outcomes (PROs) – MOS Sexual Function Scale

Lack of sexual interest	Not a problem	Little of a problem	Somewhat of a problem	Very much of a problem	Not applicable
	1	2	3	4	5

Unable to relax and enjoy sex	Not a problem	Little of a problem	Somewhat of a problem	Very much of a problem	Not applicable
	1	2	3	4	5
Difficulty in becoming sexually aroused	Not a problem	Little of a problem	Somewhat of a problem	Very much of a problem	Not applicable
	1	2	3	4	5
Difficulty in having an orgasm	Not a problem	Little of a problem	Somewhat of a problem	Very much of a problem	Not applicable
	1	2	3	4	5

XI. Patient Reported Outcomes (PROs) – Endocrine Symptoms FACT-ES

Please mark one number per line to indicate your response as it applies to the past 7 days.

	Not at all	A little bit	Some-what	Quite a bit	Very much
I have hot flashes	0	1	2	3	4
I have cold sweats	0	1	2	3	4
I have night sweats	0	1	2	3	4
I have vaginal discharge	0	1	2	3	4

I have vaginal itching/irritation	0	1	2	3	4
I have vaginal bleeding or spotting	0	1	2	3	4
I have vaginal dryness	0	1	2	3	4
I have pain or discomfort with intercourse	0	1	2	3	4
I have lost interest in sex	0	1	2	3	4
I have gained weight	0	1	2	3	4
I feel lightheaded (dizzy)	0	1	2	3	4
I have been vomiting	0	1	2	3	4
I have diarrhea (diarrhea)	0	1	2	3	4
I get headaches	0	1	2	3	4
I feel bloated	0	1	2	3	4
I have breast sensitivity/tenderness	0	1	2	3	4

I have mood swings	0	1	2	3	4
I am irritable	0	1	2	3	4
I have pain in my joints	0	1	2	3	4

XII. Godin Leisure-Time Exercise questionnaire

Please indicate the average amount of exercise you did in the **last 7 days**.

When answering these questions, please:

- note that the main difference between the 3 questions below is the intensity of the exercise.
- if you did not do any exercise in one of the categories, please write in "0".

Considering a typical week (7 days), how many times on average did you do the following kinds of exercise for more than 15 minutes during your free time?

For example, if you did fast walking for a total of 60 minutes over the past week, you would write 4.

	Times Per Week
STRENUOUS EXERCISE	
What is strenuous? HEART BEATS RAPIDLY, SWEATING (e.g. running, jogging, hockey, soccer, squash, cross country skiing, vigorous swimming, vigorous long distance bicycling, vigorous aerobic dance classes)	

	Times Per Week
MODERATE EXERCISE	
What is moderate? NOT EXHAUSTING, LIGHT PERSPIRATION (e.g. fast walking, easy bicycling, baseball, tennis, volleyball, easy swimming)	

	Times Per Week
MILD EXERCISE	
What is mild? MINIMAL EFFORT, NO PERSPIRATION	

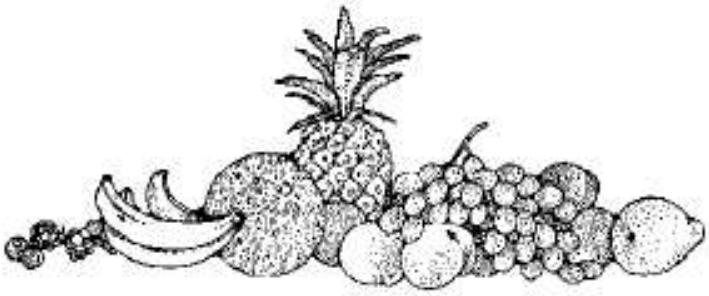
(e.g. easy walking, yoga, archery, bowling, golf)

XIII. Nutritional survey

The following represents the questions to be incorporated in the PatientViewPoint online modules, as taken from the National Institutes of Health's "Eating at America's Table Study" (quick food scan).

OMB# 0925-0450 EXP. DATE: 07/31/2000

NATIONAL INSTITUTES OF HEALTH
EATING AT AMERICA'S TABLE STUDY
QUICK FOOD SCAN



- The person who completed the telephone interviews for the Eating at America's Table Study should fill out this questionnaire.
- Use only a No. 2 pencil.
- Be certain to completely blacken in each of the answers, and erase completely if you make any changes.
- Do not make any stray marks on this form.
- When you complete this questionnaire, please return it in the postage-paid envelope to:

  National Cancer Institute
  EPN, Room 313
  6130 Executive Blvd., MSC 7344
  Bethesda, MD 20892-7344

BAR CODE LABEL HERE

NOTIFICATION TO RESPONDENT OF ESTIMATED BURDEN

Public reporting burden for this collection of information is estimated to average 15 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Office, 6701 Rockledge Drive, MSC 7730, Bethesda, MD 20892-7730, ATTN: PRA (0925-0450). Do not return the completed form to this address.

PLEASE DO NOT WRITE IN THIS AREA

SERIAL

INSTRUCTIONS

- Think about what you usually ate last month.
- Please think about all the fruits and vegetables that you ate last month. Include those that were:
  - raw and cooked,
  - eaten as snacks and at meals,
  - eaten at home and away from home (restaurants, friends, take-out), and
  - eaten alone and mixed with other foods.
- Report how many times per month, week, or day you ate each food, and if you ate it, how much you usually had.
- If you mark "Never" for a question, follow the "Go to" instruction.
- Choose the best answer for each question. Mark only one response for each question.

1. Over the last month, how many times per month, week, or day did you drink **100% juice** such as orange, apple, grape, or grapefruit juice? **Do not count** fruit drinks like Kool-Aid, lemonade, Hi-C, cranberry juice drink, Tang, and Twister. Include juice you drank at all mealtimes and between meals.

○ Never (Go to Question 2)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

1a. Each time you drank **100% juice**, how much did you usually drink?

○ Less than ¾ cup (less than 6 ounces)	○ ¾ to 1¼ cup (6 to 10 ounces)	○ 1¼ to 2 cups (10 to 16 ounces)	○ More than 2 cups (more than 16 ounces)

2. Over the last month, how many times per month, week, or day did you eat **fruit**? Count any kind of fruit—fresh, canned, and frozen. **Do not count** juices. Include fruit you ate at all mealtimes and for snacks.

○ Never (Go to Question 3)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

2a. Each time you ate **fruit**, how much did you usually eat?

○ Less than 1 medium fruit	○ 1 medium fruit	○ 2 medium fruits	○ More than 2 medium fruits
	OR		
○ Less than ¼ cup	○ About ¼ cup	○ About 1 cup	○ More than 1 cup

3. Over the last month, how often did you eat **lettuce salad (with or without other vegetables)**?

○ Never (Go to Question 4)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

3a. Each time you ate **lettuce salad**, how much did you usually eat?

○ About ½ cup	○ About 1 cup	○ About 2 cups	○ More than 2 cups

4. Over the last month, how often did you eat **French fries** or **fried potatoes**?

○ Never (Go to Question 5)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

4a. Each time you ate **French fries** or **fried potatoes**, how much did you usually eat?

○ Small order or less (About 1 cup or less)	○ Medium order (About 1½ cups)	○ Large order (About 2 cups)	○ Super Size order or more (About 3 cups or more)

5. Over the last month, how often did you eat **other white potatoes**? Count **baked, boiled**, and **mashed potatoes, potato salad**, and **white potatoes that were not fried.**

○ Never (Go to Question 6)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

5a. Each time you ate **these potatoes**, how much did you usually eat?

○ 1 small potato or less (¾ cup or less)	○ 1 medium potato (¾ to 1 cup)	○ 1 large potato (1 to 1½ cups)	○ 2 medium potatoes or more (1½ cups or more)

6. Over the last month, how often did you eat **cooked dried beans**? Count **baked beans, bean soup, refried beans, pork and beans** and **other bean dishes.**

○ Never (Go to Question 7)	○ 1-3 times last month	○ 1-2 times per week	○ 3-4 times per week	○ 5-6 times per week	○ 1 time per day	○ 2 times per day	○ 3 times per day	○ 4 times per day	○ 5 or more times per day

6a. Each time you ate **these beans**, how much did you usually eat?

○ Less than ½ cup	○ ½ to 1 cup	○ 1 to 1½ cups	○ More than 1½ cups

2

7. Over the last month, how often did you eat **other vegetables**?

DO NOT COUNT:
- Lettuce salads
- White potatoes
- Cooked dried beans
- Vegetables in mixtures, such as in sandwiches, omelets, casseroles, Mexican dishes, stews, stir-fry, soups, etc.
- Rice

COUNT:
- All other vegetables—raw, cooked, canned, and frozen

○ Never (Go to Question 8) ○ 1-3 times last month ○ 1-2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 times per day ○ 3 times per day ○ 4 times per day ○ 5 or more times per day

7a. Each of these times that you ate **other vegetables**, how much did you usually eat?

○ Less than ½ cup ○ ½ to 1 cup ○ 1 to 2 cups ○ More than 2 cups

8. Over the last month, how often did you eat **tomato sauce**? Include tomato sauce on pasta or macaroni, rice, pizza and other dishes.

○ Never (Go to Question 9) ○ 1-3 times last month ○ 1-2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 times per day ○ 3 times per day ○ 4 times per day ○ 5 or more times per day

8a. Each time you ate **tomato sauce**, how much did you usually eat?

○ About ¼ cup ○ About ½ cup ○ About 1 cup ○ More than 1 cup

9. Over the last month, how often did you eat **vegetable soups**? Include tomato soup, gazpacho, beef with vegetable soup, minestrone soup, and other soups made with vegetables.

○ Never (Go to Question 10) ○ 1-3 times last month ○ 1-2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 times per day ○ 3 times per day ○ 4 times per day ○ 5 or more times per day

9a. Each time you ate **vegetable soup**, how much did you usually eat?

○ Less than 1 cup ○ 1 to 2 cups ○ 2 to 3 cups ○ More than 3 cups

10. Over the last month, how often did you eat **mixtures that included vegetables**? Count such foods as sandwiches, casseroles, stews, stir-fry, omelets, and tacos.

○ Never ○ 1-3 times last month ○ 1-2 times per week ○ 3-4 times per week ○ 5-6 times per week ○ 1 time per day ○ 2 times per day ○ 3 times per day ○ 4 times per day ○ 5 or more times per day

**Thank you very much for completing this questionnaire.
Please return it in the enclosed, postage-paid envelope or to the address listed on the front page.**

3

ID # Place Label Here

NATIONAL CANCER INSTITUTE
QUICK FOOD SCAN

1. Think about your eating habits over the past 12 months. About how often did you eat or drink each of the following foods? Remember breakfast, lunch, dinner, snacks, and eating out. Blacken in only one bubble for each food.

TYPE OF FOOD	Never	Less than Once Per Month	1-3 Times Per Month	1-2 Times Per Week	3-4 Times Per Week	5-6 Times Per Week	1 Time Per Day	2 or More Times Per Day
Cold cereal	○	○	○	○	○	○	○	○
Skim milk, on cereal or to drink	○	○	○	○	○	○	○	○
Eggs, fried or scrambled in margarine, butter, or oil	○	○	○	○	○	○	○	○
Sausage or bacon, regular-fat	○	○	○	○	○	○	○	○
Margarine or butter on bread, rolls, pancakes	○	○	○	○	○	○	○	○
Orange juice or grapefruit juice	○	○	○	○	○	○	○	○
Fruit (not juices)	○	○	○	○	○	○	○	○
Beef or pork hot dogs, regular-fat	○	○	○	○	○	○	○	○
Cheese or cheese spread, regular-fat	○	○	○	○	○	○	○	○
French fries, home fries, or hash brown potatoes	○	○	○	○	○	○	○	○
Margarine or butter on vegetables, including potatoes	○	○	○	○	○	○	○	○
Mayonnaise, regular-fat	○	○	○	○	○	○	○	○
Salad dressings, regular-fat	○	○	○	○	○	○	○	○
Rice	○	○	○	○	○	○	○	○
Margarine, butter, or oil on rice or pasta	○	○	○	○	○	○	○	○

2. Over the past 12 months, when you prepared foods with margarine or ate margarine, how often did you use a reduced-fat margarine?

○ DIDN T USE MARGARINE ○ Almost never ○ About 1/4 of the time ○ About 1/2 of the time ○ About 3/4 of the time ○ Almost always or always

3. Overall, when you think about the foods you ate over the past 12 months, would you say your diet was high, medium, or low in fat?

○ High ○ Medium ○ Low

scan1 6/15/00

APPENDIX F: Score Interpretation

NOTE: Please see below an example of the information to be provided to the participant upon completion of the questionnaires. This information will be also available to the providers to discuss with participants during their clinic visit.

The reports produced by the system will highlight scores that are potential 'problems' because they represent either particularly poor health, quality of life below average, or significant worsening from the last time point, as follows:

Sleep Disturbance, Physical Function, Anxiety, Depression, Pain Impact, and Fatigue:

- Higher scores represent more of what is being measured (e.g., higher scores indicate better physical function and worse fatigue).
- A score of 30-70 is considered within the expected range of an average population of patients.
- Highlighted scores are either outside of that range (less than 30 for physical function; greater than 70 for all others) or are a significant change from previous answers.

Sexual Function:

- Higher scores indicate more problems with sexual function.
- A score of less than 40 is considered to be within the expected range of an average population of patients.
- Highlighted scores are above that average range (greater than 40) or a significant increase from previous answers.

Endocrine Symptoms:

- Higher scores indicate better quality of life.
- A score of 41.3 - 76 is considered to be within the expected range for an average population of women.
- Highlighted scores are below that average range (less than 41.3) or a significant decrease from previous answers.

Godin Leisure-Time Exercise questionnaire

- For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively.
- Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula: Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light).
- For example: Strenuous = 3 times/wk. Moderate = 6 times/wk, and Light = 14 times/wk. Then, the total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99.
- Godin scale score of ≥24 is active, 14-23 is moderately active, and <14 is insufficient active or sedentary.

Statistical Considerations

Sleep Disturbance, Physical Function, Anxiety, Depression, Pain Impact, and Fatigue:

- Surveys were validated in the general population.
- All of these domains are mapped to a mean score of 50, with a standard deviation of 10.
- Highlighted scores represent a score more than 2 standard deviations from the mean (20 points) or a worsening of at least half a standard deviation (5 points).

Sexual Function:

- This survey was validated in patients with major medical problems with and without depression, and patients without medical problems but with depression.
- For this population, the mean sexual problem scores ranged from 24.48 – 43.5, with a standard deviation of 32.
- Highlighted scores represent a score that is worse than the average scores among an ill population (40 points) or a worsening of at least half a standard deviation (16 points).

Endocrine Symptoms:

- This survey was validated in female breast cancer patients undergoing a variety of hormone therapies as well as normal controls.
- This survey is mapped to a mean score of 59.7, which is the total group mean from the validated population, with a standard deviation of 9.2.
- Highlighted scores represent a score that is two standard deviations away from the mean (41.3 points) or a worsening of at least half a standard deviation (4.6 points).

APPENDIX G:
Drug Diary
Contrave should not be taken with a high-fat meal.

Check boxes if the drug is taken and list any side effects you experience. Email you drug diary weekly to ANEW@jhmi.edu.

WEEK 1: Take one pill in the morning.

Contrave	Day	Notes	Morning dose #1 tablet		DO NOT TAKE Evening dose	
			Yes	No		
Week 1	1		☐	☐		
	2		☐	☐		
	3		☐	☐		
	4		☐	☐		
	5		☐	☐		
	6		☐	☐		
	7		☐	☐		

WEEK 2: Take one pill in the morning and one in the evening.

Contrave	Day	Notes	Morning dose #1 tablet		Evening dose #1 tablet	
			Yes	No	Yes	No
Week 2	1		☐	☐	☐	☐
	2		☐	☐	☐	☐
	3		☐	☐	☐	☐
	4		☐	☐	☐	☐
	5		☐	☐	☐	☐
	6		☐	☐	☐	☐
	7		☐	☐	☐	☐

WEEK 3: Take 2 pills in the morning and 1 pill in the evening.

Contrave	Day	Notes	Morning dose #2 tablets		Evening dose #1 tablet	
			Yes	No	Yes	No
Week 3	1		☐	☐	☐	☐
	2		☐	☐	☐	☐
	3		☐	☐	☐	☐
	4		☐	☐	☐	☐
	5		☐	☐	☐	☐
	6		☐	☐	☐	☐
	7		☐	☐	☐	☐

WEEK 4: Take 2 pills in the morning and 2 pills in the evening.

Contrave	Day	Notes	Morning dose #2 tablets		Evening dose #2 tablets	
			Yes	No	Yes	No
Week 4 and onward	1		☐	☐	☐	☐
	2		☐	☐	☐	☐
	3		☐	☐	☐	☐
	4		☐	☐	☐	☐
	5		☐	☐	☐	☐
	6		☐	☐	☐	☐
	7		☐	☐	☐	☐