NRG ONCOLOGY

NRG-CC004

(ClinicalTrials.gov NCT #: **03180294***)*

PHASE III DOUBLE BLIND DOSE FINDING TRIAL OF BUPROPION VERSUS PLACEBO FOR SEXUAL DESIRE IN WOMEN WITH BREAST OR GYNECOLOGIC CANCER

Amendment 3: June 7, 2019

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This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.

Site participation limited to NRG Oncology NCORP sites and sites listed below (07-JUN-2019)

Duke University Medical Center
Memorial Sloan Kettering Cancer Center
University of Michigan Comprehensive Cancer Center
University of Oklahoma Health Sciences Center
University of California San Diego Moores Cancer Center
UCLA / Jonsson Comprehensive Cancer Center

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Bupropion	Provided	N/A	Exempt	N/A

Participating Sites (07-JUN-2019)
x U.S. (NRG Oncology NCORP and sites listed on the cover page)

Document History

	Version Date
Amendment 3	June 7, 2019
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NRG ONCOLOGY

NRG-CC004

PHASE II DOUBLE BLIND DOSE FINDING TRIAL OF BUPROPION VERSUS PLACEBO FOR SEXUAL DESIRE

CONTACT INFORMATION (07-JUN-2019)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page of the CTSU member's website located at (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at https://www.ctsu.org.		

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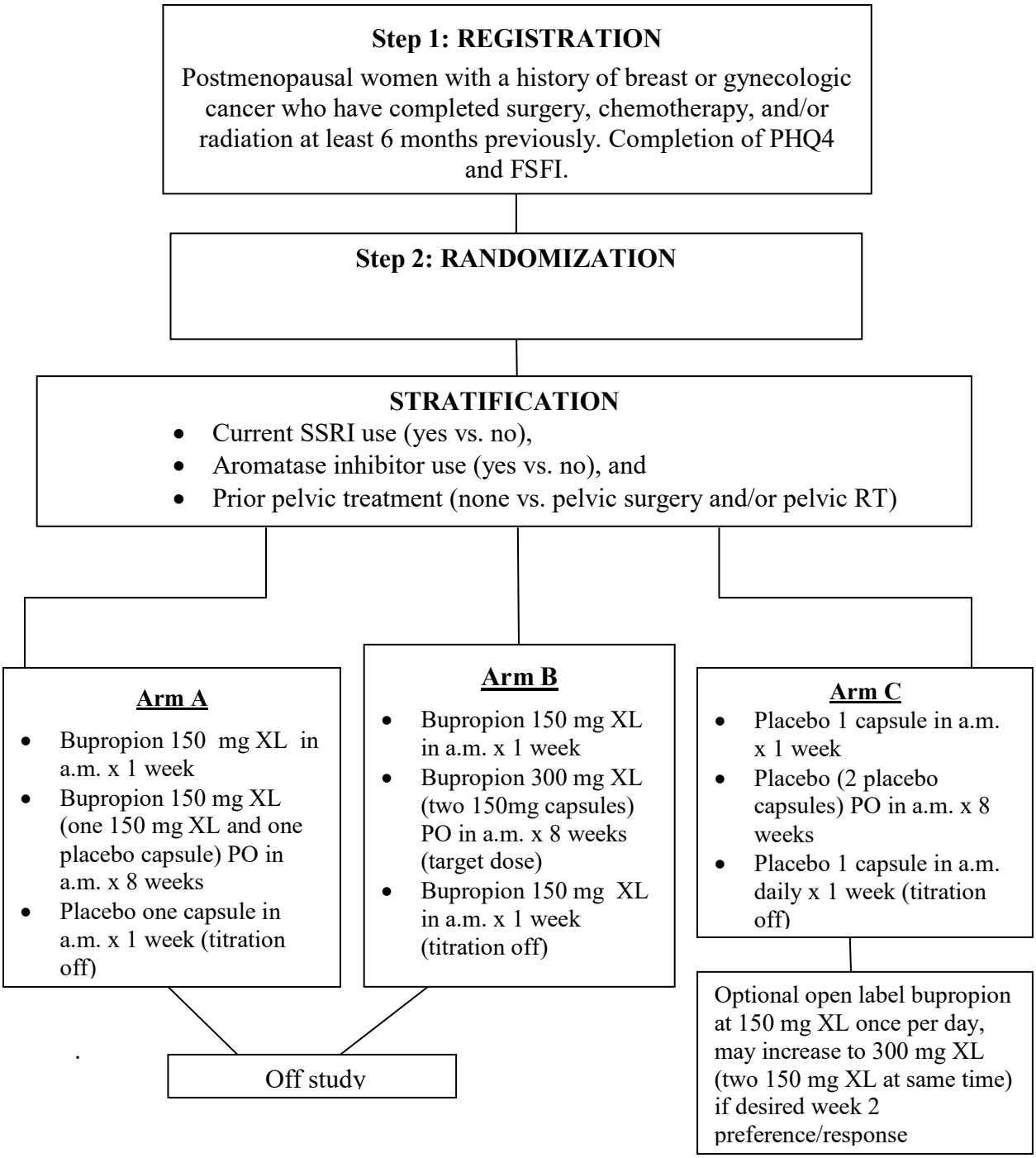
SCHEMA (08-JUN-2018)



*Pelvic surgery could be any of the following: hysterectomy, oophorectomy, salpingectomy, organ prolapse surgery, vaginal mesh implant, laproscopic removal of endometriosis, any surgical removal of endometriosis, minor debulking surgery

XL: extended release

1. OBJECTIVES

1.1 Primary Objective

Measure the ability of two dose levels of bupropion, 150 or 300 mg of extended release, to improve sexual desire more than a placebo at 9 weeks (8 weeks on the target dose) as measured by the desire subscale of the FSFI.

1.2 Secondary Objectives

1.2.1 Evaluate the side effects of 150 and 300 mg bupropion extended release and differentiate these side effects from those observed in the placebo arm.

1.2.2 Evaluate the effect of 150 and 300 mg of bupropion extended release on the PROMIS fatigue scale, PROMIS sexual desire and satisfaction measure, PHQ-4, and the FSFI total score, at 5 and 9 weeks, as well as the desire subscale score of the FSFI at 5 weeks.

1.2.3 Evaluate the effect of 150 and 300 mg of bupropion extended release on the Global Impression of Change scale and the patient's perception of risk vs. benefit at 5 weeks (4 weeks at target dose) and 9 weeks (8 weeks at target dose).

2. BACKGROUND

Prevalence and importance of female sexual health as a survivorship issue.

According to the American Cancer Society, as of January, 2014, there were 14.5 million cancer survivors (Cancer Facts & Figures 2015). Of the female survivors (7,607,230), 55% of those have been diagnosed with breast or some form of gynecologic cancer (Cancer Treatment and Survivorship Facts & Figures 2014-2015). By 2024, the number of survivors is expected to grow to 19 million, with over half of those, 9.6 million, being female. Therefore, addressing chronic negative sequelae for women in the aftermath of a cancer diagnosis and its treatments becomes a health imperative.

One prevalent consequence of treatment in some types of cancer is decreased sexual health, particularly for women with estrogen sensitive tumors due to estrogen deprivation. Sexual health can be defined as well being in relation to sexuality, which is a core aspect of humanity (WHO Reproductive Health Topics: Sexual Health 2015) The prevalence of sexual health concerns for female cancer survivors in published data ranges from 30 to 100% (Speer et al. 2015, Gilbert et al. 2011, Andersen et al. 2007, Burwell et al. 2006, Krychman and Millheiser 2013, Biglia et al. 2010) and the descriptive literature is fairly consistent demonstrating specific problems that comprise the concept of sexual health as including lubrication, dyspareunia, desire, body image, increased fatigue, and relationship concerns (Ganz et al. 1998, Carmack Taylor et al. 2004). Changes in sexual health are common after surgery, chemotherapy, radiation therapy, and endocrine therapy (estrogen inhibition), and although some studies demonstrate improvement over time, other studies reveal that negative sexual health can persist over many years (Burwell et al. 2006). The issues related to sexual health and functioning may be slightly different for survivors of breast versus gynecologic cancer, but existing literature demonstrates much overlap and almost identical importance with sexual changes being one of the most commonly reported after treatment for both groups (Burwell et al. 2006, Ganz and Greendale 2007). Perhaps most importantly, sexual function is important enough for female cancer survivors that they continue to be sexually active despite significant discomfort. A 5-year longitudinal study by Malinovszky showed that women with breast cancer note continued decline in pleasure and increase in pain with

intercourse over 5 years despite a return to usual sexual activity by 2 years (Malinovszky et al. 2006). These data provide support for the idea that sexual behavior is a necessary part of life that women may engage in despite pain and reduced pleasure. Efforts to improve this scenario are needed.

The Principal Investigator of this concept has a program of research to improve sexual health outcomes in female survivors of breast and gynecologic cancer, as sexual related issues are similar in these two female cancer groups. Since female sexual health is a multi-component concept that is influenced by the various specific symptoms reviewed in the paragraph above (self-image, vaginal atrophy, desire, relationships and fatigue), a multi-faceted approach is warranted. This is supported by an inspirational early editorial by Dr. Ganz (Ganz and Greendale 2007) stating that as sexual desire, responsiveness and satisfaction, in essence sexual health, can be affected by numerous things, when attempting to evaluate treatment, several issues must be considered. Therefore, the study represented in this proposal is one of 4 interventions being tested for related components of sexual health that together will comprise a multi-component intervention targeted toward 4 known prevalent predictors of sexual health in female cancer survivors: vaginal atrophy, self-image, sexual desire and partner concerns. Dr. Barton already completed a study addressing vaginal atrophy (Alliance N10C1) and is currently recruiting women for a randomized phase II study evaluating hypnosis for self-image. The study proposed in this concept addresses the construct of sexual desire and if this study is positive, it will be added to other effective treatments for the above mentioned predictors to provide a comprehensive approach to sexual health that can be individualized to meet a woman's needs.

What is sexual desire?

There is a lot of controversy in the literature about what constitutes female sexual desire, often called libido (Bancroft 2005, van Anders 2012). It is clear that sexual desire/libido in women is multifactorial and more complex than the similar concept in men, where there is more of a linear relationship between arousal and desire. In women, the relationship is not linear and it is confounded by relationships and self-image (Basson, 2004). It is also likely true that sexual desire may be a bit more complex in women with a cancer history compared to women without cancer. Specifically, in the cancer literature when exploring female sexual health, there is, conceptually, support that energy (perhaps fatigue) plays a role in sexual health and declines as a result of a cancer diagnosis and treatment (Wilmoth et al. 2004). Data from our recent vaginal Dehydroepiandrosterone (DHEA) study demonstrate that at baseline, vitality explained 13% of overall sexual function (unpublished data). In addition, at baseline, women in our vaginal DHEA study reported vigor/energy levels right around the 50% point (53 out of 100 with higher numbers being better) on the vitality subscale of the Medical Outcomes Scale Short Form-36. Further, linear regression modeling of overall sexual function at baseline found vitality to be a significant predictor ($p=.001$) in addition to the variables of relationship, severity and bother of vaginal symptoms, and chemically induced menopause (unpublished data).

Other studies report findings consistent with ours (WHO Reproductive Health Topics: Sexual Health 20015, Ganz 1998, Carmack Taylor 2004, Ganz and Greendale 2007). In another investigation evaluating sexual outcomes in women with a history of gynecologic

cancer, fatigue (measured with the Fatigue Symptom Inventory-revised) was significantly correlated with both sexual responsiveness and global satisfaction as measured by the Female Sexual Function Index and the Global Sexual Satisfaction Scale, respectively, all well validated measures (Carpenter et al. 2009). Based on the aforementioned data, we are conceptualizing sexual desire as a term that incorporates having the motivation and necessary energy to want to engage in sexual intimacy activity, not only intercourse.

There is also controversy about the role of testosterone in female sexual desire. (Bancroft 2005, van Anders 2012). The most commonly studied intervention that has been found effective in women with hypoactive sexual desire disorder (HSDD) without cancer has been transdermal testosterone. However, this intervention has not been effective in improving sexual desire/libido in women with a history of cancer (Barton et al. 2007). In research performed by Dr. Barton, testosterone was not found to be effective in improving libido in female cancer survivors (Barton et al. 2007) despite significant increases in testosterone concentrations and contrary to evidence of its benefit in women with hypoactive sexual desire disorder **(**HSDD) or women post menopause (Braunstein et al. 2005, Buster et al. 2005, Chudakov et al. 2007, Davis et al. 2008, Davis et al. 2006, Goldstat et al. 2003, Nathorrst-Boos et al. 2006, Shifren et al. 2000, Shifren et al. 2006, Simon et al. 2005). In addition, translational data from that clinical trial demonstrated a lack of significant association between testosterone and sexual health outcomes (Barton, Loprinzi et al. 2007).

However, the neurotransmitter, dopamine, has been better characterized than testosterone as potentially having a role in sexual motivation or desire in women (Bancroft 2005, Frohlich et al. 1999, Hull et al. 1999). Specific areas of the brain have been found to be associated with sexual desire, including the medial preoptic nucleus, nucleus accumbens, and the ventral tegmental area. This has been substantiated in functional MRI studies evaluating brain function in HSDD compared to women with no such history (Bianchi-Demicheli 2011, Arnow et al. 2009). The neurotransmitters that are active in these areas and believed to be important in reward-motivation and pleasure are dopamine, norepinephrine, oxytocin and melanocortin (Versace et al. 2013). In fact, dopamine is thought to be essential in order to promote excitatory neural inputs that are needed for behavior involving motivation. Therefore, sexual desire is not simply a response to being aroused; it is embedded in a neural response that involves memory, pleasure and emotion and is influenced by positive cues as well as inhibition of nonsexual cues (Brom et al. 2014).

2.1 Preliminary data supporting dopamine reduction with estrogen deprivation.
Animal and human data provide evidence that estrogen deprivation is associated with a loss of dopamine. In one study, after 30 days, estrogen deprivation per ovariectomy in primates resulted in over a 30% decrease in dopaminergic cells in the substantia nigra (Hull et al. 1999). In a study comparing ovariectomized rats with and without estrogen replacement, estrogen deprivation reduced striatal dopamine release and locomotor activity while estrogen replacement improved both locomotor activity and dopamine release (Bianchi-Demicheli 2011). Finally, a study in postmenopausal women was conducted to evaluate the impact of estrogen therapy on dopaminergic activity. Investigators evaluated dopaminergic tone using a measured response of growth hormone to apomorphine, which is a validated measure of dopamine tone. Women receiving estrogen therapy had a higher dopaminergic response

compared to women who were not receiving estrogen (Arnow et al. 2009).

There are further data to support that inflammatory conditions may have overlap with neurologic processes that involve dopamine (Dantzer et al. 2014). The relationship is complex, but simply put, areas of the brain that are rich with dopaminergic neurons have also been found to be impacted by inflammation (Felger and Miller 2012). Hence, dopamine function can be impacted by inflammation (Felger and Miller 2012). Interferon alpha therapy is used in these studies to simulate inflammatory processes. In a study in rhesus monkeys, after 4 weeks of interferon therapy, dopamine release was reduced when measured by both in vivo microdialysis and PET neuroimaging (Felger et al. 2013). An investigation performed by Capuron and colleagues demonstrated the same results after 6 weeks of interferon alpha administration given to medically stable adults with hepatitis C virus (Capuron et al. 2012). Hence, investigators successfully linked pro-inflammatory cytokine activity (a biomarker profile associated with fatigue which has also been associated with women diagnosed with breast cancer who have fatigue) with decreased activation of brain areas associated with reward and decreased dopamine.

In summary, these data support the hypothesis that women post cancer treatment who are estrogen deficient may have reduced dopaminergic activity that negatively impacts their sexual desire. This situation may be compounded by persistent fatigue that is also associated with increased inflammation, which may also be impacting dopaminergic areas of the brain. Treatment with a dopaminergic agent may improve sexual motivation outcomes and may also, secondarily, improve fatigue. *Our working hypothesis is that fatigue may mediate sexual desire, however, the mechanism of interest is dopamine, not inflammation, and the primary outcome of interest is sexual desire, not fatigue.*

2.2 Preliminary data with dopaminergic agents.

Despite compelling physiologic data linking dopamine to reward stimuli, motivation and reward centers that are critical to sexual desire and data associating estrogen depletion with reduced dopamine activity, dopaminergic agents have not been rigorously studied for sexual desire in female cancer survivors. In fact, one concern is that few dopaminergic agents have a side effect profile conducive to use in a supportive care trial.

Bupropion is a dopaminergic agent worth evaluating with promise to improve sexual desire in women with a history of cancer. It is an antidepressant that is chemically distinct as an inhibitor of dopamine and noradrenaline reuptake (GlaxoSmithKline 2011). Bupropion is approved for seasonal affective disorder, major depressive disorder (Micromedex Healthcare Series 2008), and smoking cessation.(GlaxoSmithKline 2015). It has been available in the US since 1989 as an immediate release formulation, with the sustained release formulation becoming available 2003 (Fava et al. 2005). Bupropion has been used in sexual medicine clinics to reverse the lack of libido instigated with the use of selective serotonin reuptake inhibitor (SSRI) antidepressants. There are limited, but promising, data to support rigorous phase II trials to evaluate whether a dose of bupropion would be beneficial to women with a history of cancer in boosting sexual desire/energy/motivation without causing intolerable or undesirable side effects (Clayton et al. 2006, Croft et al. 1999, Gitlin et al. 2002, Safarinejad 2011, Segraves et al. 2004, Mathias et al. 2004, Moss et al. 2006).

There have been several studies of bupropion in women without cancer with decreases in sexual desire. At least four of these studies were randomized placebo controlled trials and all demonstrated positive effects of bupropion on sexual desire and other domains of sexual function (Clayton et al. 2006, Croft et al. 1999, Gitlin et al. 2002, Safarinejad 2011, Segraves et al. 2004). One well-designed double blind trial recruited patients with depression and randomized them to bupropion plus sertraline placebo, sertraline plus bupropion placebo or double placebos (Croft et al. 1999). The bupropion dose used was 150 mg to 400 mg per day of the slow release formula. About 40% of the patients in each arm also had sexual desire disorder, but normal sexual functioning. By day 42, significantly fewer patients on bupropion still had sexual desire disorder compared to both the sertraline and placebo, despite both antidepressant groups experiencing significant and clinically meaningful improvements in their depression (Croft et al. 1999). Of note, there was also significantly less orgasmic dysfunction in the group receiving bupropion, similar to that in the placebo group, and significantly less than the sertraline group. In a randomized placebo-controlled trial of 218 women who were premenopausal and experiencing decreased libido from treatment with SSRI's, bupropion sustained relaease (SR) 150 mg BID versus placebo was evaluated over 12 weeks, as adjunctive treatment to their current SSRI antidepressant. The Female Sexual Function Index (FSFI) questionnaire was used as the primary endpoint. Statistically significant improvements in every domain of sexual function were seen in this study compared to placebo, with the exception of pain (Safarinejad 2011), with sexual desire improving the most of all domains. The sexual desire subscale improved from 2.2 (below the cut off indicating dysfunction) to 4.1 (above the cut off indicating normal desire). Significant improvement in the FSFI desire subscale began at the 4 week data point, improved further at 8 weeks and improved slightly more at 12 weeks. In this study, depression was already managed with the SSRI, so the bupropion/placebo was intended to target the physiological changes caused by the SSRI that negatively impacted sexual desire.

Two studies have been completed in a cancer population. In 20 women with breast cancer, an open label trial evaluated 150 mg daily of bupropion for 8 weeks for improvement in sexual function. By 4 weeks, women had a mean score on the Arizona Sexual Experience Scale that was below the cut off for dysfunction, despite baseline values being above the dysfunction cutoff. This improvement was maintained at week 8. The overall improvement on the measure was 20% (Mathias et al. 2006). The second study in 21 breast cancer survivors evaluated bupropion at a dose of 150 to 300 mg per day for fatigue, depression and quality of life (Moss et al. 2006). Bupropion significantly improved fatigue and depression after 4 weeks of a stable dose of bupropion. The study did divide the sample into depressed versus non-depressed participants using a cut-off score of >17 on the Hamilton Depression Rating Scale. When they examined fatigue improvement in this non-depressed group (N=12), there were still significant improvements on the total Brief Fatigue Inventory (BFI) and interference subscales (total score at baseline 6.5, at 4 weeks 4.5, p=.03). Therefore, the impact of fatigue in this study does not appear to be secondary to improvement in depression.

Recently, a new dopamine and norepinephrine reuptake inhibitor, flibanserin, was approved by the FDA to improve hypoactive sexual desire disorder in premenopausal women, but has not been studied in female cancer survivors (Sprout Pharmaceuticals 2015). Flibanserin was

however studied in preclinical models and several human clinical trials that began to be published in 2012. It gained FDA approval in early summer of 2015 based on three phase III randomized controlled trials (Katz et al. 2013, Thorp et al. 2012, Derogatis et al. 2012) with co-primary endpoints of sexually satisfying events and the desire subscale of the FSFI.

The positive results and subsequent FDA approval of flibanserin supports the proof of concept that dopaminergic agents may improve sexual desire. However, flibanserin was only studied in premenopausal women with hypoactive sexual desire disorder, which is likely physiologically and psychosocially, a very different situation than women with a history of cancer who are postmenopausal and severely estrogen deficient. There are a few other reasons why flibanserin is not being suggested as the dopaminergic agent to be studied in this proposal.

First, the approved dose had a withdrawal rate in all three studies of 25-30%, half due to adverse events (Sprout Pharmaceuticals 2015). The most common adverse events were dizziness, somnolence, nausea, fatigue and insomnia. This would be a particularly unwanted side effect profile in women with a history of cancer who already likely have fatigue that is contributing to their lack of sexual desire. To use an agent that can cause somnolence or fatigue is in direct contradiction to our hypothesis that fatigue is the mediating factor for sexual desire in a population of female cancer survivors. Second, there appears to be theoretically, one key difference in the mechanism of flibanserin and bupropion. That difference is that flibanserin is believed to increase dopamine and norepinephrine, but also to decrease serotonin (Sprout Pharmaceuticals 2015), whereas bupropion is not thought to affect serotonin (GlaxoSmithKline 2015, Fava et al. 2005). This difference may contribute to the undesirable side effect profile of flibanserin related to fatigue and somnolence (as these are symptoms of low serotonin). This may also be important in a population of estrogen deficient female cancer survivors as low serotonin may also be the etiology behind hot flashes and therefore, this population may already be serotonin deficient. Therefore, evaluating a drug with the intended mechanism of action (dopamine and norepinephrine inhibitor) but without additional unwanted activity (decreasing serotonin), a drug without sedating properties that is FDA approved for other indications, a drug with a long history of use without significant problems, and a drug that is available generically and thus more cost effective, would be of more interest.

To this end, we plan to evaluate two doses of bupropion versus a placebo in postmenopausal women with a history of breast or gynecologic cancer and low desire to see if there are positive effects in these populations without unwanted side effects. As demonstrated in the trials with flibanserin (listed in the section “sample and power analysis”) and Dr. Barton’s earlier trial evaluating transdermal testosterone for sexual desire (Barton et al. 2004) there is a placebo effect present in this research. Therefore, in order to evaluate whether a phase III trial is warranted, it is critical that this phase II dose finding study include a placebo arm in order to better determine the estimated effect of both doses of bupropion. This study is seeking a positive risk/benefit balance for women struggling with decreased sexual desire and will evaluate an effect size, dose, and the best primary endpoint to guide a larger definitive phase III clinical trial.

3. PATIENT SELECTION, ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the NRG web site).

3.1 Patient Selection Guidelines

Although the guidelines provided below (in Section 3.1.1) are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological and cognitive ability and general health that permits completion of the study requirements and required follow up.

3.2 Eligibility Criteria (08-Jun-2018)

Prior to Step 1 Registration

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Score of <9 on the PHQ-4.

3.2.2 Patients must have a FSFI desire subscale baseline score less than 3.3

NOTE-Both the PHQ4 and FSFI must be completed by the patient and data entered in OPEN at Step 1 registration to determine eligibility within 10 days prior to registration. Both of these scores will be calculated in the OPEN system once submitted as part of Step 1 registration. An error message will appear once you begin Step 2 registration if one or both of the scores make the patient ineligible. In this situation, continue to complete Step 2 with the reason the patient will not continue on the study as "Other" and specify ineligible.

3.2.3 Diagnosis of breast or gynecologic cancer, all types (examples are DCIS, LCIS, invasive breast, ovarian, endometrial, vulvar, cervical and vaginal);

3.2.4 Completed definitive therapy consisting of surgery, chemotherapy or radiation therapy at least 180 days ago (may continue on Herceptin or endocrine therapy);

3.2.5 Post-menopausal as defined by at least ONE of the following:

- 12 months (365 days) without a period,
- Bilateral oophorectomy;
- Chemically induced menopause as long as there are no plans to stop during the study;
- For women 57 and under, if at least one ovary and woman has had hysterectomy, must have FSH (>30mIU/mL) and estradiol in menopausal range per institution's laboratory (generally that is <10 for ultra sensitive assay: <25-30 otherwise); (Note: women 58 and older do not have to have hormonal tests)
- At least one ovary intact, with a uterus, and 180 days without a period with FSH (>30mIU/mL) and estradiol in menopausal range per institution's laboratory (generally that is <10 for ultra sensitive assay: <25-30 otherwise) (Note: women 58 and older do not have to have hormonal tests);;

3.2.6 Age ≥ 18;

3.2.7 History, Physical and Performance Status of 2 or less within 180 days prior to registration.

3.2.8 Adequate renal and hepatic function

- AST and ALT ≤ 2.5x ULN
- Total bilirubin ≤1.5x ULN
- Glomerular filtration rate >60ml/min. OR ≤ ULN creatinine per institution normals

3.2.9 For breast cancer patients only, endocrine therapies are allowed (such as aromatase inhibitors, **but not current tamoxifen. Prior tamoxifen is permitted with a 30 day wash out period**).

3.2.10 Vaginal estrogen is allowed, for all protocol disease sites, if dose equal to or less than that in estring (<7.5 mcg) and it has been used for at least 30 days with no plans to stop or alter use during the course of the study.

3.2.11 Antidepressants for mood and hot flashes, including SSRI's (that are not CYP2D6 substrates) will be allowed if patients have been on for the last 60 days and the dose is not expected to change during the course of the study. Only subthreshold or low dose antidepressants will be allowed, not antidepressants that have been titrated up to the highest doses for depression management (examples but not a comprehensive list are Lexapro 5-10 mg, Celexa 10 – 20 mg and Effexor –up to 75 mg is allowed).

3.2.12 The patient must provide study-specific informed consent prior to study entry/screening.

3.2.13 Women who report that their motivation/desire for sexual intimacy has decreased since her cancer diagnosis.

3.2.14 Able to swallow whole capsules.

3.2.15 Proficient in English (due to number of questionnaires not validated in other languages).

3.2.16 Completion of the FSFI and PHQ4. Both questionnaries will be required and data entered at the time of step 1 registration.

Prior to Step 2 Randomization

3.2.17 Completion of the following baseline quality of life forms: PHQ4, FSFI, PROMIS sexual function and satisfaction, PROMIS fatigue short form 8a, Impact of Treatment Scale, PRO-CTCAE items, and Revised Dyadic Adjustment Scale. These quality of life forms will be required and **data must be entered in RAVE at step 2 registration**. If available at the time of step 1 registration, step 2 registration can take place immediately after step 1, but cannot occur more than 30 days after step 1. ***Women who do not currently have a partner do not have to complete the Revised Dyadic Adjustment Scale. Enter "no partner" for this form.***

3.3 Ineligibility Criteria (9/8/17)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Diagnosis of depression, Major Depressive Disorder (MDD), suicidal ideations or anxiety disorders in the past 5 years per the medical chart based on DSM IV diagnoses.

3.3.2 Seizure disorders

3.3.3 Current or history of anorexia or bulimia in the past 5 years

3.3.4 Allergy to bupropion

3.3.5 Use of drugs primarily metabolized by CYP2D6; these are called CYP2D6 substrates. This is because bupropion is a strong CYP2D6 inhibitor so it will decrease the rate of metabolism of drugs that are CYP2D6 substrates (see Appendix I for a PARTIAL list of drugs and resources to look up drugs)

3.3.6 Stage IV cancer
3.3.7 History of Parkinson's Disease, multiple sclerosis or fibromyalgia
3.3.8 Extensive pelvic exenteration surgery, surgeries which include partial or total vaginectomy with or without reconstruction; radical vulvectomy with or without remove of clitoris
3.3.9 Women who are currently undergoing or planning to undergo reconstruction surgery during the course of the study. Women who have completed reconstruction surgery must be 30 days from surgery.
3.3.10 Oral or transdermal estrogen therapy is not allowed
3.3.11 Males are not permitted to participate
3.3.12 Patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbituates, and antiepileptic drugs after chronic use
3.3.13 Patients who discontinue MAO-I's within 14 days prior to starting the investigational drug
3.3.14 Poorly controlled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg) on three or more readings in the past 12 months.
3.3.15 Patients with active bipolar disorder
3.3.16 Patients with impaired decision making as determined by the treating physician
3.3.17 Concurrent use of bupropion
3.3.18 Concomitant invasive malignancy requiring treatment other than non-melanomatous skin cancer.
3.3.19 Previous or concurrent use of flibanserin.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

PRE-TREATMENT ASSESSMENTS (07-Jun-2019)
Prior to Step 1 Registration

Assessments	Prior to Step 1 Registration (calendar days)
Diagnosis of breast or gynecologic cancer (DCIS, LCIS, invasive breast, ovarian, endometrial, vulvar cervical and vaginal)	X
Completed definitive therapy consisting of surgery, chemotherapy and/OR radiation therapy (patients may continue on Herceptin, endocrine therapy or perjeta)	X (180 days)
Post menopausal as defined in Section 3.2.5	X (365 days)
History/Physical/Performance Status	X (180 days)
Concomitant medication review	X (14 days)
Adequate renal and hepatic function (See Section 3.2.8)	X (180 days)
PHQ4* and Female Sexual Function Index (FSFI)	X (10 days)

Prior to Step 2 Registration

Assessments	Prior to Step 2 Registration
Patient Reported Ouctomes** • PRO-CTCAE • PROMIS sexual function and satisfaction • PROMIS fatigue short form 8a • Impact of Treatment Scale • Revised Dyadic Adjustment Scale	X (Need to be completed and data entered at Step 2 Registration)

*See Appendix III for details on how to report emergent and non-emergent issues related to PHQ-4 scoring and reporting. If participants score 6-8 on the PHQ-4 at any of the time points, they should be offered mental health resources (see Appendix III). If participants score 9 or higher, they should receive an immediate referral for an assessment (see Appendix III).

**Patient reported outcomes are recommended to be completed at the time of consenting and at step 1 visit. They can also be completed at the time of step 2 as the PHQ4 and FSFI must be uploaded and reviewed in order for the patient to move on to step 2.

ASSESSMENTS DURING TREATMENT

Assessments	Week 1	Week 2	Week 5	Week 7	Week 9
Female Sexual Function index			X		X
PROMIS sexual function and satisfaction			X		X
PROMIS fatigue short form 8a			X		X
PHQ-4			X		X
Global Impression of Change and satisfaction with treatment					X
PRO-CTCAE*	X	X	X	X	X
Solicited Adverse Event Assessment (CTCAE)**	X	X	X	X	X
Collection of study drug dose	X	X	X	X	X
Adverse Event Assessment#	X	X	X	X	X
Concurrent Medications	X	X	X	X	X
Risk Benefit Form					X

*PRO-CTCAE and **CTCAE should be completed at the end of week 1, 2, and 7 in addition to weeks 5 and 9 to ensure patient is tolerating the study drug. These questionnaires may be completed by telephone, mail or an office visit and documented in the patient's record. Patients who consent to VisionTree will complete the PRO-CTCAE form in VisionTree Optimal Care (VTOC).

Adverse Event Assessments (CTCAE) will be collected by telephone or an office visit.

ASSESSMENTS FOR PATIENTS CONTINUING ON BUPROPION (See Appendix II)

Assessments	Week 4 and 8 (if patient continues on bupropion)
Female Sexual Function Index	X
PHQ-4	X
PROMIS fatigue short form 8a	X
PROMIS sexual function and satisfaction	X
Adverse Event Assessment	X

Patient-Reported Outcomes

All patient-reported outcomes completed during and after treatment should be completed within the following timeframes:

- Week 1 (day 7) during treatment: Days 5-11 during treatment
- Week 2 (day 14) during treatment: Days 12-23 during treatment
- Week 5 (day 35) during treatment: Days 30-41 during treatment
- Week 7 (day 49) during treatment: Days 44-55 during treatment
- Week 9 (day 63) during treatment: +/- 1 week (days 56-70)
- Week 4 during open label: +/- 1 week
- Week 8 during open label: +/- 1 week

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Two doses of bupropion XL, 150 and 300 mg, will be tested over 8 weeks at the target dose as a response has been seen within that time frame; however, we will evaluate effects at 5 weeks (4 weeks at the target dose) as a secondary outcome to evaluate time to benefit for a larger, well powered study.

The drug will be titrated and taken as described below. There will be a one week titration, 8 weeks at the target dose, and one week titration off of the drug. Patients should be instructed that the study drug needs to be increased and decreased slowly, over one week, and therefore doses should not be skipped nor should their assigned treatment be stopped abruptly. Any issues with tolerating or staying on the study drug should be discussed with their study doctor.

5.1 Study agent (08-Jun-2018)

Protocol treatment must begin within 21 days after randomization.

5.1.1 Study drug and placebo will be identical looking capsules. Patients will be randomized to treatment arm, A, B, or C. Each arm will have a designated study treatment kit that will contain 4 bottles labeled 1, 2A and 2B, and 3. All patients in each arm will follow the exact same procedure for taking their assigned treatment. A patient instruction sheet will be included in each kit. Instruct patients to read and follow the directions carefully. Patients should also be instructed to call the research personnel if they have any intolerance and wish to stop the study drug. Patients should not stop the medication on their own and they should not alter the number of pills taken.

The study agent will be taken orally for a total of 10 weeks according to the treatment arm assignment below. **Do not chew, cut or crush the tablets.**

Arm A

Days 1-7 (1 week): Bupropion 150mg XL every morning. Patients will take one capsulefrom bottle marked 1.

Days 8-63 (8 weeks): Bupropion 150mg XL and one placebo capsule every morning.Patients will take one capsule from the bottle marked 2A and one capsule from the bottle marked 2B.

Days 64-70 (1 week): Placebo capsule every morning (tritration off week). Patients will take one capsule every morning from the bottle marked 3.

Arm B

Days 1-7 (1 week): Bupropion 150mg XLevery morning. Patients will take one capsule every morning from the bottle marked 1.

Days 8-63 (8 weeks): Bupropion 300mg XL every morning. Patients will take one capsule form the bottle marked 2A and one capsule from the bottle marked 2B for a daily dose of 300mg.

Days 64-70 (1 week): Bupropion 150 XL every morning (titration off week). Patients will take one capsule every morning from the bottle marked 3.

Arm C

Days 1-7 (1 week): One placebo capsule every morning. Patients will take one capsule from the bottle marked 1.

Days 8-63 (8 weeks): Two placebo capsules every morning. Patients will take one capsule from the bottle marked 2A and one capsule from the bottle marked 2B.

Days 64-70 (1 week): One placebo capusule every morning (titration off week). Patients will take one capsule every morning from the bottle marked 3.

Patients who have been on the placebo arm can be offered the opportunity to receive bupropion 150 or 300 mg XL for a total of 8 weeks. This includes a week to titrate up and a week to titrate down if the desired dose is 300 mg XL. See Appendix II for further details.

5.2 General Concomitant Medication and Supportive Care Guidelines (08-Jun-2018)

5.2.1 Prohibited Therapies

- Oral or transdermal estrogen.
- Medications metabolized by CYP 2D6 as in Appendix I, such as tamoxifen, other SSRIs.
- Flibanserin

5.2.2 Participation in Other Trials

Participation in other symptom trials is allowed as long as the trial does not focus on the management of sexual health or fatigue in any way.

5.3 Emergency Unblinding Procedure (08-Jun-2018)

The decision to break the unblinding code must be based on a serious adverse event unexpected for the study drug and related to the study drug or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment. The blind ordinarily should be broken for unexpected adverse events related to the study drug (e.g., safety reports submitted to the FDA and all participating investigators). All cases that are emergently unblinded must be reported to the NCI Central IRB (CIRB).

Sites can call NRG Headquarters during business hours (8:30 AM to 5 PM ET), at 215-574-3150 and ask to speak to the Supporting Study Statistician. For after hours, weekends, and holidays, call 215-940-8902.

Optional Open Label Phase

Patients who have been on the placebo arm can be offered the opportunity to receive bupropion 150 or 300 mg XL for a total of 8 weeks. This includes a week to titrate up and a week to titrate down if the desired dose is 300 mg XL. NRG Headquarters will unblind patients on the placbo arm only once all study data has been submitted. Patients who were randomized to the placebo arm will have a new form located in the week 10 folder in Rave called "Patient Crossover" once all data has been submitted for all nine weeks. If the patient decides to crossover and has previously consented to participate in VisionTree, the RA must go back into the patient's Vision Tree account and activate the placebo template See Appendix II for further details.

5.4 Duration of Therapy

For the double-blind portion of the study in the absence of treatment delays due to adverse event(s), treatment may continue as specified, over 10 weeks, or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 7
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Drug Discontinuation (08-Jun-2018)

Drug must be discontinued for patients who have documented allergic reaction at any grade. Due to the nature of the blinding, drug cannot be dose reduced and due to the nature of bupropion and the need to titrate, drug cannot be stopped and restarted. Hence, participants who experience any grade 1, 2 or 3 (expected) event **that is not tolerable** will have study drug discontinued upon discussion between the provider and participant. Grade 3 unexpected events attributable to the study drug will result in permanent study drug discontinuation. Any grade 4 event will result in permanent study drug discontinuation.

Patients who wish to stop therapy due to intolerable side effects or any other desire to withdraw early from the study will need to titrate off of the study drug. For instances of early treatment discontinuation, NRG will not reveal treatment assignment but will require all patients taper off study drug by one capsule from bottle 3 for one week and then can stop the study drug.

CTCAE 5.0 Grade	Action
Grade 1, 2 or 3 (expected)	Discontinue study drug for any adverse events that participants find not tolerable after discussion between the provider and participant.
Grade 3 unexpected and attributable to study drug	Discontinue study drug permanently
Grade 4, 1st appearance	Discontinue permanently

6. TREATMENT MODIFICATIONS/MANAGEMENT (08-JUN-2018)

Due to the nature of the blinding, patients will not be allowed to modify their dose. If patients are experiencing unwanted side effects, they may discontinue study drug as outlined in Section 5.5.

If a patient forgets to take their morning dose, but remembers within 6 hours, they can still take their assigned dose. If it is over 6 hours, they should wait until the next day. Patients should NOT take extra doses.

During the phone contact time points described in section 7.3.1, assess the tolerability of any reported adverse events. Discontinue the study drug per section 5.5.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Commercial Agents

The commercial agents in NRG-CC004 are bupropion 150mg XL.

7.2 Adverse Events and Serious Adverse Events (08-Jun-2018)

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs

reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for all AE reporting, CTEP-AERS reporting and case report forms. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018. All study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

7.3 Adverse Events for Commercial Study Agents (08-Jun-2018)

Refer to the package insert for detailed pharmacologic and safety information

Side effects at doses of 300 mg/day (XL or SR formulation) with a prevalence of 5% or greater are listed: headache (XL 34%, SR 26%, plac 23%), nausea (XL & SR 13%, plac 8%), dry mouth (XL 26%, SR 17%, plac 7%), constipation (XL 9%, SR 10%, plac 7%), insomnia (SR 11%, plac 6%), infection (plac 6%, SR 8%, XL 9%) and diarrhea (plac 6%, SR 5%, XL 7%) and dizziness (XL 6%, SR 7%, plac 5%) (GlaxoSmithKine 2011, Micromedex Healthcare Series 2008, GlaxoSmithKline 2015, Fava et al. 2005, Dailymed). In addition, bupropion can be associated with anorexia, resulting in 5 pound weight loss in studies for about 23% of participants versus 11% on placebo, the XL is associated with nasopharyngeal effects (13% versus 12% placebo) and the SR formulation is associated with tremors (6% versus 1% in placebo).

Note the black box warning for suicidal thoughts and behaviors in patients being treated for depression and neuropsychiatric reactions in patients taking bupropion sustained release for smoking cessation. Please see the package insert for a detailed discussion of the black box warning.

The following adverse events must be reported expeditiously: any grade psychiatric serious adverse events

7.3.1 Solicited Adverse Events and PRO-CTCAE

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol

can be found on the forms section of the CTSU protocol webpage and is titled "NRG-CC004 NCI PRO-CTCAE Item Library." PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action

Collect the following solicited adverse events (CTCAE v.4): tremor, dizziness, insomnia, headache, dry mouth, anorexia, nausea, constipation, nasal congestion and pharyngolaryngeal pain.

The patient will complete the PRO-CTCAE items dizziness, insomnia, headache, dry mouth, decreased appetite, nausea, constipation and the RA will assess for the solicited AEs (CTCAE v. 4 items) at phone contact points with the patient. This will include at the end of weeks 1, 2, 5, 7 and 9. These phone call points are associated with key events in the study. The end of week 1 is to evaluate the ability to titrate to the assigned dose. Even though the CRA will be blinded, it will be important for study personnel to contact patients at the end of week 1 to evaluate whether they experienced any unwanted effects that would result in their unwillingness to continue with the study. The end of week 2 coincides with being at the target dose and this contact is again to evaluate whether there are tolerance issues. The end of week 5 is a time when some secondary endpoints need to be completed so this contact will serve as that reminder as well as AE evaluation. The end of week 7 contact will encourage continued engagement in the study and the end of week 9 is the end of the study when the measures will also need to be completed.

Solicited Adverse Events CTCAE v. 4	PRO-CTCAE Iterms with (Attributes)
Dizziness	Dizziness (severity, interference)
Insomnia	Insomnia (severity, interference)
Headache	Headache (frequency, severity, interference)
Dry mouth	Dry mouth (severity)
Anorexia	Decreased appetite (severity, interference)
Nausea	Nausea (frequency, severity)
Constipation	Constipation (severity)
Tremor	
Nasal congestion	
Pharyngolaryngeal pain	

7.4 Expedited Reporting of Adverse Events (08-Jun-2018)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited

adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Biostatistical/Data Management Center by phone, (number to be provided). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 5 days. Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. For instructions to submit supporting documentation to the NRG Oncology at 1-215-574-3191.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events

Any Phase Study Utilizing a Commercial Agent[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 3	Grade 4		Grade 5	
	Unexpected	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely				10 day	10 day

Possible Probable Definite	10 day	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

Inclusions to expedited reporting: any grade psychiatric serious adverse events.

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

8. INVESTIGATOR REGISTRATION AND STUDY ENTRY PROCEDURES (07-JUN-2019)

8.1 Registration and Study Entry Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1.1 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the

network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-CC004 Site Registration

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- Study Agent Shipment Form (SASF) (see section 8.1.3); and
- Compliance with all protocol-specific requirements (PSRs)

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist.

8.1.2 Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-CC004*;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.1.3 Pre-Registration Requirements for the Initial Shipment of bupropion

All site pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a SASF available on the NRG web site. The completed SASF document must be submitted to the CTSU via the Regulatory Submission portal (sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab).

8.2 Patient Enrollment (08-Jun-2018)

Patient registration and randomization can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the

CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration at websupport@acr.org or call the NRG Registration Desk at 215-571-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9.0 DRUG INFORMATION

9.1 Commercial Agent (08-Jun-2018)

Sites must refer to the package insert for detailed pharmacologic and safety information.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

9.1.1 Adverse Events

Please refer to the package insert and Section 7.3.

9.1.2 Availability/Supply (07-JUN-2019)

Bupropion 150 mg XL and Matching Placebo will be distributed by a vendor Clinical Research Services, a division of RxCrossroads by McKesson.. The investigator, or responsible party designated by the investigator, must maintain a careful record of the receipt, distribution, and return of all drugs received from Clinical Research Services according to good clinical practices.

The Study Agent Shipment Form (SASF) must be submitted to the CTSU Regulatory Office via the Regulatory Submission Portal as soon as the individual responsible for the study agent has been identified. The SASF is available on the NRG website.

The drug supply will not be shipped by Clinical Research Services until the patient has been randomized. NRG Oncology will notify Clinical Research Services to initiate each of these shipments after randomization of the patient. Clinical Research Services will ship drug for patients randomized to Arm A, Arm B, and Arm C. Patients will receive a supply of Bupropion 150 mg XL or Matching Placebo for the entire treatment (Days 1-70). Each patient will receive one kit that contains 4 bottles labeled 1, 2A, 2B and 3 as well as a patient instruction sheet. If a patient requires additional study drug for any reason, the site will need to contact Clinical Research Services directly to request additional study drug. In addition, Clinical Research Services will ship open label bottles to the site for patients who were on placebo and register for the open label phase (see Appendix II for additional details).

Upon notification of a new patient enrollment, Clinical Research Services will place an outbound call to the site contact to confirm that the site's shipment is being processed. Clinical Research Services' distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables Clinical Research Services to mitigate potential delivery delays.

Clinical Research Services will ship drug to sites in the U.S., according to the following schedule:

NRG-CC004 Shipment Schedule				
Patient Randomized	Initial e-order sent by NRG Oncology	Initial e-order received by CRS (before 2 pm ET)	Initial order shipped by CRS	Initial order received at site

Monday	Monday	Monday	Monday	Tuesday
Tuesday	Tuesday	Tuesday	Tuesday	Wednesday
Wednesday	Wednesday	Wednesday	Wednesday	Thursday
Thursday	Thursday	Thursday	Thursday	Friday
Friday	Friday	Friday	Friday	Monday

Drug deliveries are restricted during weekends and holidays. Clinical Research Services observes the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Please contact the drug distributor listed in the protocol directly for shipment tracking information and anticipated delivery dates or if a shipment has not been received by the expected date.

At the completion of the study, unused supplies will be destroyed at the site according to the institution's policy for drug destruction. A drug destruction form is available on the NRG website. Please complete and send the form to Clinical Research Services (see below for contact information).

Questions about supply and delivery should be directed to:

Clinical Research Services, a division of RxCrossroads by McKesson
845 Regent Blvd.
Suite 100B
Irving, TX 75063
Email: clinicalresearchservices@mckesson.com
Toll Free: 800-693-4906

10. PATHOLOGY/BIOSPECIMEN

Not applicable for this trial.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Patient Reported Outcomes and Toxicity Measures (08-Jun-2018)

All measures can be found on the NRG Oncology website under the protocol specific page. All scoring, including at registration, will be conducted by NRG Oncology.

Female Sexual Function Index (Weigel, Meston and Rosen 2005)
The Female Sexual Function Index is a relatively brief measure (19 items) that has been developed and validated to be used across the age range of women, including postmenopausal women. Its conceptualization came out of an evolving understanding of female sexual functioning in recent years. It is a multi-dimensional measure that covers the major domains of female sexual functioning including desire, arousal, satisfaction and orgasm. Additionally, it addresses lubrication and pain. Its discriminate validity is based

on its ability to differentiate women diagnosed with female sexual arousal disorder from normal controls. The FSFI looks at measures of both frequency and desire in each domain as well as satisfaction in most domains. The desire subscale consists of two items and has a range of 1.2 to 6 when scored. A cut off for less than normal desire has been determined to be less than 3.3. The FSFI has been used in both intervention and epidemiologic studies. The FSFI has been validated across a wide range of sexual problems, with the most recent Cronbach alpha's being over 0.9 for internal reliability. A score of 26.55 (from a range of 2 to 36) was found to be the cut point to distinguish women with and without sexual dysfunction (lower scores indicating sexual dysfunction). The FSFI has also been used with female gynecologic cancer survivors and was used in the Alliance N10C1 study that accrued mostly women with breast cancer (Carpenter et al. 2009). This measure will be completed at baseline, 5 and 9 weeks. For open label patients it will be completed in weeks 4 and 8.

PROMIS Sexual Health Measure (Flynn et al. 2013)
The PROMIS initiative or Patient Reported Outcomes Measurement Information System is a large effort supported by the National Institute of Health to improve measurement science related to self-reported health measures. There are numerous PROMIS measures in various stages of development and psychometric testing. To the extent possible, investigators are urged to use PROMIS measures to have some capability to compare across trials. The sexual function and satisfaction measure is one PROMIS tool that has good content, face, discriminant, and convergent validity, and is, therefore, ready to be incorporated into clinical trials. In particular, for women, it demonstrates good convergent validity with the FSFI, which is considered the gold standard measure in sexual function. However, PROMIS is shorter and easier to score. In this study, the following will be used: the global satisfaction domain with 6 items (correlation of 0.76 with the FSFI satisfaction subscale) and interest domain with 4 items (correlation of 0.84 with the FSFI desire subscale) with one question about interfering factors; fatigue, for a total of 11 items. PROMIS was created in such a way that investigators can use items that are relevant to the population and the research question while maintaining validity. This measure will be completed at baseline, 5 and 9 weeks.For open label patients it will be completed in weeks 4 and 8.

PROMIS Fatigue 8
Fatigue will be measured with the PROMIS short form 8a. This questionnaire contains 8 questions related to severity, bother and activity interference related to fatigue. Responses are "not at all" to "very much" for 6 questions; and "never" to "always" for two questions. The perspective is in the last 7 days. The PROMIS measures have demonstrated good reliability and validity with a subset of 7 items correlating with the full fatigue item bank (95 items), with a correlation coefficient of r=0.76 and correlations with the FACIT-F of 0.95. Even though the vitality subscale of the SF-36 was used in the previous vaginal symptom study and shown to significant predict variance in sexual health, the PROMIS fatigue correlated with the vitality subscale of the SF-36 with a correlation coefficient of r=0.89, so this scale should be able to capture what is needed for this study (Cella et al. 2010). This will be completed at baseline, 5 and 9 weeks. For open label patients it will be completed in weeks 4 and 8.

PHQ-4
The PHQ 4 was developed from the PHQ-9 and GAD-7 to be an ultra-brief screening tool for depression and anxiety disorders (Kroenke 2009). It has been validated in the general population and found to be comparable to the PHQ-8 (Lowe 2010). Scores on the PHQ-4 range from 0 to 12, with scores 0-2 being normal, 3-5 indicating mild symptoms, 6-8 moderate symptoms and 9-12 severe. Cronbach's alpha for the 4 items was 0.85. The PHQ-4 was strongly correlated with the mental health subscale of the SF 20 (r=.80) and social functioning (r=.52). These correlation coefficients were nearly identical to those of the PHQ-8 (Kroenke 2009). This will be completed at baseline, 5 and 9 weeks. For open label patients it will be completed in weeks 4 and 8.

Global Impression of Change (Sloan et al. 2002, Sloan et al. 2006)
The Subject Global Impression of Change is a 7-point item in which the participant rates the change in the sexual desire since beginning the study (ranging from "very much better," "moderately better," "a little better," "about the same," "a little worse," "moderately worse," to "very much worse"). It has been used extensively for determination of minimally clinically significant differences in numerous oncology clinical trials. Two questions will be asked using the 7-point response scale, one on overall sexual desire and the other on energy/fatigue level.

Additional risk/benefit investigator developed questions will be included. The first is "How satisfied are you with the impact of the study drug on your sexual desire? "not at all," "a little," "somewhat," "quite a bit," "very much" and the second question will be, "Were the benefits of this treatment greater than any side effects you may have experienced?" (yes or no). This form will ONLY be completed at the end of the study, at 9 weeks.

Side effect measures
Patients will complete PRO-CTCAE items and the Clinical Research Associates (CRAs) will complete CTCAE items plus the PRO-CTCAE items at phone contact points with the patients. This will include at the end of weeks 1, 2, 5, 7 and 9. These phone call points are associated with key events in the study. The end of week 1 is to evaluate the ability to titrate to the assigned dose. Even though the CRA will be blinded, it will be important for study personnel to contact patients at the end of week 1 to evaluate whether they experienced any unwanted effects that would result in their unwillingness to continue with the study. The end of week 2 coincides with being at the target dose and this contact is again to evaluate whether there are tolerance issues. The end of week 5 is a time when the primary endpoint and some secondary endpoints need to be completed so this contact will serve as that reminder as well as AE evaluation. The end of week 7 contact will encourage continued engagement in the study and the end of week 9 is the end of the study when the measures will also need to be completed.

Impact of Treatment Scale
This scale is a measure of body change stress and was developed by investigators at The Ohio State University. It was developed and tested specifically in women with breast

cancer and then edited and tested in women with gynecologic cancer. It has demonstrated good reliability and validity in both samples, with Cronbach alphas over .90 (Frierson, Thiel and Andersen 2006). It was able to discriminate between women with lower and higher satisfaction with their sexual life (Frierson, Thiel and Andersen 2006). This measure is being included only at baseline, as body image is one of the known predictors of sexual health.

Revised Dyadic Adjustment Scale

This is a 14-item scale that measures relationship functioning and has been recently used in a study of breast cancer survivors. The instrument provides an overall adjustment score as well as subscale scores for cohesion, consensus and satisfaction. Overall scores range from 0 to 69, with lower scores indicating more relationship problems. Work has been accomplished to establish a cut off score of <41 to screen for poor relationships (Rowland et al. 2009). The scale has demonstrated good validity confirmed through factor analysis and reliability. Cronbach's alpha coefficients are .81 for the consensus subscale, .85 for satisfaction and .80 for cohesion. The total scale score has a Cronbach's alpha coefficient of .90 (Busby et al. 1995). The Revised Dyadic Adjustment Scale will be completed at baseline only.

11.2 Optional Online Completion of Patient-Reported QOL Assessments (9/8/17)

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This technology allows consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data."

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

For this trial, the baseline QOL forms must be completed in hardcopy (on paper) prior to the start of treatment. In addition, should the patient cross over and continue to weeks 14 and 18, then the Female Sexual Function Index, the PHQ-4, the pROMIS fatigue short form 8a, the PROMIS sexual function and satisfaction must be completed in hardcopy (on paper). To complete subsequent QOL forms online, patients will be asked for an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.

Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient's e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: "*Your Quality of Life forms for the study, NRG-xxxxx, are now due. Please go to http://www.optimalcare.com, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study."* The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). The first reminder will be sent at the beginning of the "window" to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the 7 QOL time points (following the baseline QOL forms, which are completed in hardcopy, and including the optional open label portion for women receiving placebo). After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point.

The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

12. DATA AND RECORDS

12.1 Data Management/Collection (07-JUN-2019)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and
    - To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Collection of Quality of Life Questionnaires

Patients will be permitted to complete questionnaires at the study site or at home. For convenience, patients can be given stamped, self-addressed envelopes in which to mail completed questionnaires back at 5 and 9 weeks.

12.2 Summary of Data Submission

Patients will complete PRO-CTCAE items and the Clinical Research Associates (CRAs) will complete CTCAE items at phone contact points with patients. This will include at the end of weeks 1, 2, 5, 7 and 9. These phone call points are associated with key events in the study. The end of week 1 is to evaluate the ability to titrate to the assigned dose. Even though providers will be blinded, it will be important for study personnel to contact patients at the end of week 1 to evaluate whether they experienced any unwanted effects that would result in their unwillingness to continue with the study. The end of week 2 coincides with being at the target dose and this contact is again to evaluate whether there are tolerance issues. The end of week 5 is a time some secondary endpoints need to be completed so this contact will serve as that reminder as well as AE evaluation. The end of week 7 contact will encourage continued engagement in the study and the end of week 9 is the end of the study when the measures will also need to be completed including the primary endpoint.

The AE data will be entered into the RAVE using the standard RAVE AE form. Keep a source documentation for the AE collection in the patient's record.
Summary of Data Submission: Refer to the NRG website

12.3 Data Quality Portal (07-JUN-2019)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a prospective, randomized, double-blinded, placebo-controlled phase II trial will determine which Bupropion dose, if any, will move to a phase III trial. Patients will be stratified by current SSRI use (yes vs. no), prior pelvic treatment (none vs. pelvic surgery and/or pelvic RT), and aromatase inhibitor use (yes vs. no) and then randomized 1:1:1 to receive a150XL target dose of Bupropion, a 300 XL target dose of Buproprion, or placebo. The target accrual is 234 patients and patients will be analyzed according to the intent-to-treat principle using all enrolled at-risk patients.

13.2 Study Endpoints

13.2.1 Primary Endpoint

Change in sexual desire, as measured by the desire subscale of the Female FSFI, from baseline to 9 weeks

13.2.2 Secondary Endpoints

- Adverse events, including PRO-CTCAE
- Fatigue, as measured by PROMIS fatigue scale
- Sexual desire, as measured by the desire subscale of the FSFI at 5 weeks and PROMIS sexual desire and satisfaction measure at 5 and 9 weeks
- Sexual functioning, as measured by the FSFI total score
- Depressive mood, as measured by the PHQ-4
- Patient's perception of change, as measured by the Global Impression of Change scale, and risk vs. benefit

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis and Endpoints

The primary hypothesis is the intervention (Bupropion 150 XL or 300XL) will result in improved sexual desire, as measured by the sexual desire subscale of the FSFI, greater than that of the placebo.

13.3.2 How Primary Endpoints Will Be Analyzed

The primary endpoint, change from baseline to 9 weeks in FSFI desire subscale (sum of questions 1 and 2 on the FSFI), will be tested between both bupropion arms and the control arm using a t-test with each comparison having a 1-sided significance level of 0.05. Effect sizes between placebo and each treatment arm will be reported. The desire subscale will be scored at each data point according to the scoring guidelines. The change score will be calculated as baseline subtracted from follow-up score. Longitudinal trends in FSFI desire subscalewill be assessed using a mixed effects model with maximum likelihood estimation on the mean scores with treatment arm, treatment by time interaction, baseline FSFI desire subscale score, and PROMIS fatigue score as covariates to assess the impact of treatment and fatigue. Other covariates of interest are stratification factors (SSRI use, prior pelvic treatment and aromatase inhibitor use),

sociodemographic variables [age, race, disease type, current treatment, partner status, time since diagnosis, (<5 years, 5-10 years, >1 year) and BMI], baseline impact of treatment scale score, and baseline revised dyadic adjustment scale score. Since the revised dyadic adjustment scale is to be completed only by patients with a partner, separate models will be run with and without this covariate as the sample size will be decreased when this variable is included. Inclusion of the impact of treatment scale allows for controlling the influence of body image on sexual desire. Inclusion of the revised dyadic adjustment scale score will allow control of potential confounding of effect of partner issues.

Each FSFI subscale score will be assessed for confounding the treatment effect of on desire. General linear models (GLMs) will be used to assess this with FSFI desire subscale change score as the dependent variable separately at 5 and 9 weeks with other relevant subscale scores (arousal, lubrication, orgasm, and pain) at the corresponding time point as an independent variable along with baseline FSFI desire subscale score and treatment arm. For the model with pain, whether the patient has clitoral and labial pain and an interaction between clitoral or labial pain and FSFI pain subscale score will also be included as independent variables. If any of these subscales shows evidence of confounding, they will be incorporated into the main FSFI desire subscale model described above.

Missing data will be assessed. If ≥15% of the data is missing at any time point for the FSFI desire subscale score, patient characteristics will be compared between patients with completed assessments and those with missing assessments. Graphical methods may also be used to determine the type of missingness. If the missingness is determined to be ignorable, no additional analyses need to occur. If the missingness is determined to be non-ignorable, other methods, such as imputation and pattern mixture models, may be performed.

Since the FSFI desire subscale consists of only 2 items, an assessment of floor and effects will be performed. Counts and frequencies of patients who experienced floor effects will be provided by arm for each time point of FSFI collection. This will be done to inform the phase III trial if bupropion appears to be helpful. Due to the eligibility criteria of patients scoring < 3.3 on the desire subscale at baseline, ceiling effects will not occur.

In order to move forward with a phase III study evaluating bupropion for sexual desire, at least one dose of bupropion would need to result in statistically significant improvement over placebo as measured by the desire subscale of FSFI. This bupropion dose would need to meet the following criteria:

- be absent of grade 4+ SAE's attributable to treatment
- ≤ 20% of patients on the bupropion arm of interest would not have stopped protocol treatment based on AE's

If both doses equally improve sexual desire as measured by the FSFI desire subscale, the dose that meets the above criteria would move forward. If both doses meet the above criteria, then the lower dose will move forward to the phase III trial.

If neither dose meets the desired effect size but less than or equal to 20% of patients have not terminated treatment early and there are no grade 4 SAE's attributable to study treatment, then an analysis will be conducted to determine the effect of the assigned treatment in those patients who score in the "normal" range of the dyspareunia subscale, dyspareunia subscale score > 3. Specifically, a general linear model will be performed with desire subscale change score at 9 weeks as the dependent variable and treatment arm, dyspareunia (as a binary variable) at 9 weeks, and a treatment by dyspareunia interaction as independent variables. If there is a clear signal that a bupropion dose has a positive impact when vaginal atrophy symptoms are less severe, it can be argued that bupropion should be studied further. In other words, a lack of effect in the entire population could be confounded too much by vaginal atrophy symptoms. To make vaginal atrophy an exclusion, however, would make the study nearly impossible to recruit to. The overall plan for this research is to identify effective interventions for various components of sexual health. In clinical practice, as these treatments are implemented, it would be expected that if a woman had low desire and vaginal atrophy symptoms, that both would be treated, which would be the plan for the phase III trial.

13.3.3 Sample Size and Power Calculations

The primary endpoint of this trial is the change in FSFI desire subscale score from baseline to 9 weeks. The FSFI is the current gold standard for the measurement of female sexual health and it contains a validated subscale specific to sexual desire. This was one of the outcomes used in the FDA approved drug, flibanserin, for Hypoactive Sexual Desire Disorder (HSDD). Since there is limited data using this drug in this patient population, an effect size will be used to calculate the sample size. Cohen's widely used guidelines for interpreting the magnitude of difference define 0.8 standard deviation (SD) as a "large" effect size, 0.5 SD as a "medium" effect size, and 0.2 SD as a " small" effect size (Cohen 1988). In this trial looking for a signal to move forward to a phase III trial, a small to moderate effect size of 0.45 will be used. Studies in different patient populations and those using different interventions, such as flibanserin, have shown similar effect sizes (DeRogatis 2012) with recent meta-analysis demonstrating an effect size of 0.4 (Jaspers 2016). Using a two sample t-test with a one-sided type I error of 0.05 (overall type I error of 0.1 after a Bonferroni correction) and an effect size of 0.45, 62 patients/arm will be needed to achieve 80% statistical power. **After adjusting for 20% non-compliance, 234 patients will be enrolled in this trial.**

13.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

13.5 Accrual/Study Duration Considerations

This study will only be open to NRG Oncology NCORP sites. Previous randomized controlled trials for vaginal symptoms and sexual desire have been completed in a timely fashion in the NCORP mechanism [NCCTG now Alliance] trials N10C1 DHEA for vaginal symptoms and N02C3 Evaluation of transdermal testosterone for libido). The

DHEA study recruited 464 women from 82 NCORP sites between July, 2011 and May, 2013. The transdermal testosterone for libido study recruited 150 women in just 8 months.

It is expected that due to regulatory processes at the site, the first 6 months after study activation will result in negligible accrual. Once sites have the study active, it is projected to accrue 10 patients/month after the initial 6 month period which results in a total study duration of approximately 2 years. During months 6-8 after activation, accrual will be monitored. If the accrual rate during this period is < 50% of the expected monthly accrual rate, the study team, with input from the NRG Oncology, DMC will evaluate whether the trial should be opened to the entire NRG Oncology membership.

13.6 Secondary or Exploratory Endpoints (including correlative science aims)

13.6.1 Secondary Hypotheses and Endpoints:

- Evaluation of adverse events, including PRO-CTCAE, specifically it is hypothesized that there will not be any grade 4+ AEs related to treatment
- Comparison of fatigue, as measured by the PROMIS fatigue at baseline, 5 and 9 weeks, between the placebo and each intervention arm and determine it's impact and association on sexual desire and sexual functioning
- Comparison of sexual desire, as measured by the desire subscale of the FSFI at baseline and 5 weeks and PROMIS sexual desire and satisfaction measure at baseline, 5 and 9 weeks, between the placebo and each intervention arm
- Comparison of sexual functioning, as measured by the FSFI total score at baseline, 5 and 9 weeks, between the placebo and each intervention arm
- Evaluation of depressive mood, as measured by the PHQ-4 at baseline, 5 and 9 weeks
- Patient's perception of change, as measured by the Global Impression of Change scale at 9 weeks, and risk vs. benefit, measured at 9 weeks, between the placebo and each intervention arm

13.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Adverse events

Adverse events (AEs) will be graded according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE) v. 5.0. Adverse events will also be assessed using PRO-CTCAE items. PRO-CTCAE items of Interest that are associated with potential drug side effects, based on the well-documented AEs of bupropion, include: tremors, dizziness, insomnia, headache, dry mouth, decreased appetite, nausea, and constipation. Counts of all AEs by grade will be provided by treatment arm. Nasopharyngeal effects will be graded using the CTCAE, two items from the Respiratory category: nasal congestion and pharyngeal pain (dryness). Patients will complete PRO-CTCAE items and providers will complete CTCAE items at the end of weeks 1, 2, 5, 7 and 9.

Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The distribution of AE grade and PRO-CTCAE score in each intervention arm will be compared to the placebo arm using a chi-square test, or Fisher's exact test if cell frequencies are < 5, at the one-sided 0.05 significance level. Missing data will be assessed as described in Section 13.3.2.

Fatigue
Fatigue, which is believed to be a potential mediator, will be measured by the PROMIS fatigue at baseline and 5 and 9 weeks from the start of treatment. The change from baseline to 5 and 9 weeks will be compared between the placebo and each intervention arm using a t-test, or Wilcoxon test if the data is non-normal, and compared at the one-sided 0.05 significance level. Spearman correlation coefficients will be used to assess the association between fatigue and sexual desire, as measured by both the sexual desire subscale of the FSFI and the PROMIS sexual desire and satisfaction measure, and sexual functioning, as measured by the FSFI total score, at each time point. Missing data will be assessed as described in Section 13.3.2.

Dyspareunia
Dyspareunia will be measured using the FSFI dyspareunia subscale score at baseline, 5 and 9 weeks. It will be assessed using a cutpoint of ≤3 (painful intercourse) vs. >3 (not painful intercourse; Wiegel 2005). The percent of patients with and without painful intercourse at each follow-up time point will be compared between the placebo and each intervention arm using a chi-square test, or Fisher's exact test if cell frequencies are < 5. In order to also assess the effect clitoral or labial pain have on painful intercourse, logistic regression will be used at each follow-up time point (ref). If one of the groups has a very small frequency of events (<5%), Firth's penalized likliehood will be used as maximum likelihood estimation may be biased (Firth 1993). Stratification factors, baseline dyspareunia (defined using the cutpoint), and other sociodemographic variables may also be considered for inclusion in the model. Missing data will be assessed as described in Section 13.3.2.

Sexual Desire
Sexual desire will be measured by the sexual desire subscale of the FSFI and the PROMIS sexual desire and satisfaction measure at baseline, 5 and 9 weeks from the start of treatment. The primary endpoint compares the change from baseline to 9 weeks using the sexual desire subscale of the FSFI. The PROMIS sexual desire and satisfaction measure was chosen to be a secondary endpoint, as it is a relatively newly validated measure for sexual health. This endpoint will include comparison of the placebo and intervention arms of the change from baseline to 5 weeks for both sexual desire tools as well as the change from baseline to 9 weeks using the PROMIS sexual desire and satisfaction measure using a t-test, or Wilcoxon test if the data is non-normal, and compared at the one-sided 0.05 significance level. A longitudinal model for the FSFI desire subscale is described in Section 13.3.2. Similarly, longitudinal trends in PROMIS sexual desire and satisfaction measure will be assessed using a mixed effects model with maximum likelihood estimation on the mean scores with treatment arm, baseline PROMIS sexual desire score, and PROMIS fatigue score as covariates to assess the impact of treatment and fatigue. Other covariates of interest are stratification factors (SSRI use and aromatase inhibitor use), sociodemographic variables (age, race, disease type, current treatment, partner status, and BMI), baseline impact of treatment scale score, and baseline revised dyadic adjustment scale score. Inclusion of the impact of treatment scale allows for controlling the influence of body image on sexual desire. Inclusion of the revised dyadic adjustment scale score will allow control of potential

confounding of effect of partner issues. Missing data will be assessed as described in 13.3.2.

Sexual Functioning
Sexual functioning will be measured using the FSFI total score at baseline, 5 and 9 weeks. The change from baseline to 5 and 9 weeks will be compared between the placebo and each intervention arm using a t-test, or Wilcoxon test if the data is non-normal, and compared at the one-sided 0.05 significance level. Longitudinal trends in FSFI total score will be assessed using a mixed effects model with maximum likelihood estimation on the mean scores with treatment arm and PROMIS fatigue score as covariates to assess the impact of treatment and fatigue. Other covariates of interest are stratification factors (SSRI use and aromatase inhibitor use), sociodemographic variables (age, race, disease type, current treatment, partner status, and BMI), baseline impact of treatment scale score, and baseline revised dyadic adjustment scale score. Inclusion of the impact of treatment scale allows for controlling the influence of body image on sexual desire. Inclusion of the revised dyadic adjustment scale score will allow control of potential confounding of effect of partner issues. Missing data will be assessed as described in Section 13.3.2.

Depressive Mood
Depressive mood will be measured using the PHQ-4 at baseline, 5 and 9 weeks. Depressive mood at each time point will be compared between the placebo and each intervention arm using a t-test, or Wilcoxon test if the data is non-normal, and compared at the one-sided 0.05 significance level. Since bupropion is an anti-depressant, it is expected that patients on the bupropion arms will have improved mood as compared to those on placebo. Spearman correlation coefficients will be used to assess the association between depressive mood and sexual desire, as measured by both the sexual desire subscale of the FSFI and the PROMIS sexual desire and satisfaction measure, sexual functioning, as measured by the FSFI total score, and fatigue, as measured by the PROMIS fatigue, at each time point. If depressive mood is found to be associated with sexual desire, it will be considered in the longitudinal model for sexual desire using the FSFI desire subscale. Missing data will be assessed as described in Section 13.3.2.

Patient's perception of change and risk vs. benefit
The Global Impression of Change will be assessed by dividing responses into two categories: positive response (patients reporting "a little better to very much better") and negative response (patients reporting "the same to very much worse"). This is measure will be used assess the degree of perceived benefit patients had from the study agent. This will help to explore the clinical significance of the statistical changes on the primary and secondary endpoints such as sexual desire and sexual functioning. Assessment of the patient's perception of risk vs. benefit will be performed after determining the percentage of women responding "yes" to the question about benefits being greater than the side effects and the percentage responding "somewhat" or better to the question about satisfaction with treatment. These questions will be used in the decision rule for a phase III trial. Differences between treatment arms will be tested using the chi-square test, or Fisher's exact test if cell frequencies are < 5, for these comparisons at the one-sided 0.05

significance level.

13.7 Gender/Ethnicity/Race Distribution

Since this trial is only open to NRG NCORP members, there will be no international accrual. No differences across the patient subsets below are anticipated.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	0	0	0	2
Asian	19	0	0	0	19
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	21	0	2	0	23
White	175	0	14	0	189
More Than One Race	0	0	0	0	0
Total	218	0	16	0	234

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APPENDIX I (08-JUN-2018)

Bupropion is a strong CYP 2D6 inhibitor. That means that if another drug is primarily metabolized by CYP2D6 (called a CYP2D6 substrate) then taking that drug with bupropion may impact the effect or toxicity of the drug. Therefore, it is important that you look up each participant's usual drugs to make sure they are not taking any CYP2D6 substrates. Some of the main ones are listed below but this is not a all-inclusive or comprehensive list. If you don't see a drug, nutrition or herbal supplement on this list, that doesn't mean it is ok to take with bupropion.

Please consult with a pharmacist for complete drug/drug interaction screening review.

Drugs Metabolized by CYP2D6 Enzyme

ANALGESICS	**CHOLINESTERASE INHIBITORS**
codeine	donepezil
hydrocodone	
oxycodone	**COUGH SUPPRESSANT**
phenacetin	dextromethorphan
tramadol	
	PSYCHOTROPICS
ANESTHETICS	amitriptyline
lidocaine	amphetamine
	aripiprazole
ANORECTICS	atomoxetine
dexfenfluramine	chlorpromazine
	clomipramine
ANTIEMETIC/PROKINETICS	desipramine
metoclopramide	duloxetine
ondansetron	fluoxetine
	fluvoxamine
ANTIHISTAMINES	haloperidol
chlorpheniramine	iloperidone
promethazine	imipramine
	methamphetamine
ANTINEOPLASTICS	methoxyamphetamine
tamoxifen	minaprine
	nortriptyline
CARDIOVASCULAR	paroxetine
carvedilol	perphenazine
clonidine	pimozide
diltiazem	risperidone
disopyramide	sertraline
flecainide	thioridazine
S-metoprolol	zuclopenthixol
mexiletine	
nebivolol	
propafenone	
propranolol	
sparteine	
timolol	

APPENDIX II (07-JUN-2019)

Provisions for Unblinded (Open-Label) Bupropion for Patient Enrolled in Placebo Only Arm

1.0 **Summary**

Patients receiving Arm C (placebo only) may choose to receive bupropion for 8 weeks.

1.1 Buproion will be supplied to the patient free of charge and distributed by Biologics, Inc (see Section 9.1.2 of the protocol).

1.2 **Steps to receive open-label bupropion**

1.2.1 Code breaking is completed by NRG Oncology for patients enrolled on the placebo arm only.

1.2.2 The treatment code will be supplied to the treating institution via the Patient Crossover Form in Medidata Rave by NRG Oncology immediately after all study data has been submitted to NRG Oncology. If the Patient Crossover Form appears in the Week 10 folder, then the patient was randomized to the placebo arm. If this form does not appear, then the patient was randomized to one of the two experimental arms and will not be unblinded.

1.2.3 Once the treatment code has been received by the institution, the decision to receive open-label bupropion will be made by the patient and treating physician

1.2.4 The treating institution will complete the Patient Crossover Form in the 10 week folder in Medidata Rave which will trigger an auto-generated email message to request drug be shipped by Clinical Research Services, a division of RxCrossroads by McKesson. Drug will not be provided until this form has been submitted.

Note: Treating institutions should complete the patient crossover form in Medidata Rave for all patients who received placebo. For patients who do not wish to receive bupropion the treating site should answer "no" to the question on the Patient Crossover Form.

For patients who wish to receive bupropion the treating institution should answer "yes" to the question on the Form.

If the patient decides to crossover and has previously consented to participate in Vision Tree, the RA must go back into the patient's Vision Tree account and activate the placebo template .

2.0 **Treatment Plan**

Patients will receive bupropion 150 or 300 mg XL for a total of 8 weeks. This includes a week to titrate up and a week to titrate down if the desired dose is 300 mg XL.

2.1 Patients choosing to receive bupropion will complete QOL assessments at weeks 4 and 8. See Section 4.0 of the Protocol "Assessments for Participants Continuing on Bupropion."

2.2 **Drug Information**

See Section 9 of the protocol

2.3 **Supply**

Bupropion will be supplied free of charge to the patient and distributed by Clinical Research Services, a division of RxCrossroads by McKesson. See protocol Section 9.1.2.

3.0 **Adverse Event Reporting:** See Section 7.0 of the protocol for further details.

APPENDIX III

SAFETY PLAN

PHQ-4 Assessment of Depression/Anxiety

The PHQ-4 is a screening questionnaire evaluating depression and anxiety and is included in this protocol related to eligibility, and is repeated at weeks 5 and 9. The Stage I Screening assessment will be done in person and the Stage II Follow-Up assessment will be done according to site procedures, either by phone or in person. This Safety Plan provides detailed instructions on reporting severe depression or anxiety based on the PHQ-4 screening tool. The healthcare team will be required to respond in accordance with this Safety Plan in the event that the participant scores either 6 to 8 or 9 or higher.

PHQ-4 Emergent Risk**:** further assessment for elevated anxiety or depression requiring intervention will be presumed with a score of 9 or higher.

PHQ-4 Non-emergent risk**:** Participants who score 6 to 8 will be offered a referral for further assessment and help.

Emergent Risk Policy

Participants who score 9 or higher on the PHQ-4 are required to undergo evaluation by a clinician in the patient's cancer care setting to assess degree of risk. If a participant meets criteria for this, notify clinical staff immediately that the patient requires a risk assessment prior to leaving the clinic.

Inform the participant that you are required by protocol to request further assessment based on the total score on the questionnaire.

If the participant refuses or denies acute distress, suicidality or acute anxiety, let the participant know you are required to complete a report and to notify their health care provider about the assessment result. Council the patient to contact their health care provider if they feel acute distress and to call 911.

The Informed Consent gives us permission and it is not a breech of confidentialit. Once clinical staff have been notified, your responsibility has been discharged.

The CRA must complete an Emergent Risk Incident Report (see Appendix IV) and submit it to NRG Oncology by uploading the form in Rave.

Non-Emergent Risk Policy

Staff at NRG member institutions will be required to review completed questionnaires and respond in accordance with this Safety Plan in the event that the participant scores 6-8 on the PHQ- 4. Telephone interviewers will be required to respond in accordance with this Safety Plan in the event that the PHQ-4 is scored at 6 to 8.

This policy requires the site CRA to offer referral information to the participant, to offer assistance to the participant in obtaining further evaluation and treatment, and completion of a

Non-Emergent Risk Incident Report. Participants should be offered resources at the site where they are receiving cancer care (if available) or elsewhere as well as community resources.

The CRA must complete the Non-Emergent Risk Incident Report (see Appendix V) and submit it to NRG Oncology by uploading the form in Rave.

APPENDIX IV
Emergent Risk Incident Report

Note: This form must be submitted within 1 business day after completion of the questionnaire and/or interview.

Case Number:

Date:

What triggers Emergent Risk?

Score on PHQ-4 of 9 or greater requires completion of the Emergent Risk Incident Report and following the safety plan outlined in appendix III.

Did participant agree to contact with clinical staff for further assessment?

☐ Yes ☐ No

On-Site Clinical Personnel Contacted:

Name of On-Site Clinical Staff:
☐ Yes _____Time of contact
☐ No

Did participant desire contact information for counseling or other mental health treatment?
☐ Yes ☐ No

Was information provided? ☐ Yes ☐ No

Signature of Site CRA: Date:

Check one:

☐ Pre-randomization

☐ Week 5

☐ Week 9

Upload the completed form in Rave.

APPENDIX V
Non-Emergent Risk Incident Report

Note: This form must be submitted within 2 business days after completion of the questionnaire and/or interview.

Case Number:

Date:

Participant scored 6 to 8 on PHQ-4:

Did participant desire contact information for counseling or other mental health treatment?
☐ Yes ☐ No

Was information provided? ☐ Yes ☐ No

Signature of Site CRA: Date:

Check one:

☐ Pre-randomization

☐ Week 5

☐ Week 9

Upload completed form in Rave.