Placebo-controlled trial of bupropion for smoking cessation in pregnant women

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Study Summary

Title	Placebo-controlled trial of bupropion for smoking cessation in pregnant women
Short Title	Bupropion Study
Protocol Number	*820364*
Phase	Phase II
Methodology	This is a prospective, placebo-controlled RCT of the efficacy and safety of bupropion in combination with behavioral counseling for smoking cessation during pregnancy. Pregnant smokers (N=360) will receive bupropion or placebo treatment for 10 weeks, under strict double-blind conditions.
Study Duration	Approximately 54 months
Study Center(s)	Multicenter study: University of Pennsylvania (Penn): Dickens Women's Health Center (DWHC) at the Hospital of the University of Pennsylvania (HUP) and Pennsylvania Hospital (PAH) Thomas Jefferson University: Jefferson University Department of Obstetrics and Gynecology Associates (JOGA) and Maternal Addiction, Treatment, Education and Research Center (MATER; Jefferson) and Christiana Care Hospital System, Newark, DE.
Objectives	**Specific Aim 1:** Conduct a 10-week placebo-controlled trial of bupropion 300 mg/day in 360 pregnant smokers who are at 13–26 weeks gestation. We will monitor smoking behavior and adverse effects (AEs) of the medication during a 10-week treatment period. A post-treatment follow-up visit will be held at 24 weeks post target quit date (post-TQD). We will also provide two booster counseling sessions at weeks 2 and 6 postpartum and a final research evaluation at 24 weeks post-TQD. We will use text messages to send pregnancy-relevant information and medication-adherence cues to improve medication adherence. In addition to examining the effect of treatment on smoking cessation, we will monitor its effects on pregnancy outcomes (length of gestation, rate of pregnancy complications, and birth outcomes). **Specific Aim 2:** Assess changes in depression symptoms and craving as mediators of bupropion's effect on quit rates. **Exploratory Aim:** Explore genetic, metabolic, and social/behavioral moderators of the efficacy of bupropion on cigarette abstinence and safety. To generate new hypotheses, we will explore whether the risk of AEs and the efficacy of bupropion treatment (vs. placebo) are moderated by: 1) the rate of nicotine metabolism (i.e., nicotine metabolite ratio (NMR)] and variation in *CYP2A6*; 2) variation in *CYP2B6* and plasma concentrations of bupropion and hydroxybupropion; and 3) variation in social/behavioral variables, including weight concerns, body image, and the presence of other smokers in the home.
Number of Participants	360
Diagnosis and Main Inclusion Criteria	Pregnant Smokers who are at 13-26 weeks gestation.
Study Product, Dose, Route, Regimen	Bupropion tablets and matching calcium carbonate tablets as placebo for blinding. Maximum bupropion daily dosage is 300 mg by mouth per day. Dosing will be for 3 days at 150 mg per day and then 150 mg twice daily.
Duration of administration	10 weeks

Reference therapy	placebo
Statistical Methodology	Preliminary analyses will assess sample characteristics (e.g., age, race, study site) by treatment using t-test or contingency table methods. These variables will also be examined for their relationship to completion of outcome assessments. Variables related to treatment arm or completion of follow ups will be included as covariates in analyses of study aims. Compliance measures will be evaluated across treatment arms, and controlled for in primary analyses. We will use intent-to-treat as the primary method to evaluate study aims. For Aim 1, we will test treatment group differences in a binary abstinence outcome that is a repeated measure using a generalized estimating equations (GEE) model with a logit link. Quit rates after 10 weeks of study medication and at 24 weeks post-TQD will represent our primary outcome variables. Medication group (bupropion vs. placebo) and time point (10 and 24 weeks) will be treated as categorical predictor variables, and the model will predict separate effects of treatment on abstinence at each time point (an interaction). Mean birth weight will be compared for treatment groups using a two-sample t-test, in the context of multiple linear regression. We will also compare treatment arms for equivalence of the frequency of moderate-to-severe adverse events (individual and total). For Aim 2, we will use a regression-based path model approach to examine mediation of treatment effects by changes in depression and craving scores, which will be entered in the model as standardized pre-post differences, continuously distributed and treated as normal in linear regression. The effects of treatment arm on mediators, and of mediators on outcome, will be assessed using linear regression and standardized variables. For Aim 3, we will explore whether the risk of adverse events and the efficacy of bupropion treatment (vs. placebo) is moderated by: 1) the rate of nicotine metabolism and variation in *CYP2A6*; 2) the rate of bupropion metabolism (i.e., variation in *CYP2B6* and plasma concentrations of bupropion and hydroxybupropion); and 3) variation in social/behavioral variables, including weight concerns, body image, and the presence of other smokers in the home.

1. Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1. Background

Smoking During Pregnancy is a Major US Public Health Problem: Smoking during pregnancy is a major modifiable cause of poor pregnancy and child health outcomes in the US (1, 2). Maternal smoking increases the risk of a number of serious adverse outcomes of pregnancy, including spontaneous abortion, placental complications, preterm delivery, and fetal and neonatal death. The most consistent adverse effect of smoking during pregnancy is low birth weight (LBW, i.e., <2500 g) (1, 24, 25), the risk of which doubles with maternal smoking (2). In turn, LBW (particularly very low birth weight, i.e., <1500 g), exponentially increases morbidity and mortality risk (3). In the US, maternal smoking is responsible for 30% of LBW babies, 10% of premature deliveries, and 5% of infant deaths (7). Fortunately, smoking cessation by 16 weeks gestation (9, 10), or as late as the third trimester (10), results in a near-normal birth weight infant. Reductions in smoking also increase birth weight (26). Despite these risks, the majority of women who are smoking at the time of their first prenatal visit continue to smoke, risk factors for which include being unmarried, less educated, heavier smokers (>1/2 pack per day), depressed, with partners who smoke (27-30).

Interventions for Smoking Cessation in Pregnant Smokers:

Behavioral Interventions for Smoking in Pregnancy**:** Smoking cessation efforts in pregnant women have depended largely on behavioral interventions alone, despite consistent evidence that combining behavioral and pharmacologic strategies is more effective than either alone. A meta-analysis of 72 trials (11), including randomized controlled trials (RCTs) in over 20,000 pregnant smokers, showed a modest reduction in smoking by women who received a behavioral intervention relative to usual care [risk ratio (RR) = 0.94]. Babies born to women in the intervention groups were less likely to have a low birth weight (RR = 0.83) and to be born preterm (RR = 0.86). Mean birth weight was 53.9 g (95% CI = 10.44 g to 95.40 g) greater in the intervention groups. A review of the findings from six controlled trials with pregnant smokers of lower socioeconomic status (SES) showed that financial incentives for smoking cessation was efficacious during pregnancy and the early postpartum period, with abstinence rates several-fold those of controls (31). The intervention also improved estimated fetal growth, mean birth weight, and the percentage of low-birth-weight infants. The high cost of the incentives limits the impact of this approach, particularly in public settings with limited funding. Further, there were high relapse rates once the incentives were removed.

Behavioral interventions for smoking among pregnant women are limited by several other factors. First, they are least effective in heavier smokers, with a quit rate of 20% in pregnant women who smoke <10 cigarettes per day (CPD), 15% in women who smoke 10-19 CPD, and 5% in women who smoke >20 CPD (32). Second, they are less effective at mitigating nicotine abstinence effects (e.g., craving/withdrawal) than pharmacotherapy (e.g., bupropion; ref. 33). Pregnant women report that nicotine withdrawal symptoms and craving are major reasons for their inability to quit smoking (34). Third, behavioral interventions are generally less efficacious than pharmacotherapy in treating ND in depressed smokers (33). Upwards of 12% of pregnant women have depression (1) and upwards of 50% of depressed pregnant women smoke (8). African American pregnant smokers with elevated depression symptom scores were half as likely as women with lower depression scores (17) to consider seriously quitting smoking during pregnancy. Fourth, women with low annual incomes are half as likely as those with higher

incomes to quit smoking during pregnancy (35), with behavioral interventions of particularly low efficacy in lower SES women (36, 37). Finally, women–especially pregnant women–are faster metabolizers of nicotine (13), making them less likely to respond to behavioral smoking cessation interventions and more likely to respond to pharmacotherapy (i.e., bupropion; ref. 15).

The utility of a smoking cessation treatment in pregnant women depends on its efficacy in smokers with greater severity of ND, craving and withdrawal, a high rate of co-morbid depression, more rapid nicotine metabolism, and economic disadvantage, which characterize many pregnant smokers (38).

Pharmacologic Interventions for Smoking. Several medications are FDA approved for smoking cessation in non-pregnant smokers. Nicotine replacement therapies (NRTs) partially replace the nicotine usually derived from smoking, relieving craving and other withdrawal symptoms (39, 40). The odds ratio (OR) of abstinence with NRTs compared to placebo varies from 1.5 for the nicotine gum to 2.3 for the nasal spray (12). Bupropion, a non-nicotine medication first approved by the FDA as an antidepressant, inhibits the neuronal reuptake of dopamine and norepinephrine (41). It has an OR of 2.1 for smoking cessation (12) and has been shown to reduce depressive symptoms in smokers (42), particularly smokers with high baseline depression (52). Varenicline, an $\alpha 4\beta 2$ nicotinic receptor partial agonist (44), has an OR of 3.1 in promoting smoking cessation (12). However, there are no safety data on the use of varenicline for pregnant smokers. As discussed below, bupropion may be especially efficacious for smoking cessation in pregnant women.

Studies of NRT for Smoking Cessation during Pregnancy: In an effectiveness study (45), pregnant smokers received cognitive-behavioral therapy (CBT) and were randomly assigned to receive a choice of NRT (gum, patch, or lozenge) or no medication. Although the quit rate in the NRT group was approximately double that of the comparison group, the study was stopped because the NRT group had twice the serious adverse event (SAE) rate of the no-medication group. After adjusting for a history of preterm delivery, which was the most common SAE, the difference in SAE rate between groups was not statistically significant (p=0.09). Three efficacy studies of NRT have been conducted in pregnant smokers (46-48). In a Danish study (46), all women received counseling and either 6 weeks of a nicotine patch or placebo. At the end of pregnancy, neither quit rates nor mean CPD differed by group. However, patch compliance was poor (i.e., the average use being only 2 weeks). In a US study (47), 194 pregnant smokers were randomly assigned to receive treatment with 2 mg gum or placebo combined with individual behavioral counseling. Smoking cessation rates were non-significantly higher in the NRT group. Importantly, despite limited adherence to NRT, it produced a greater reduction in CPD and cotinine concentrations than placebo and was associated with better treatment retention. Mean (SD) birth weight [3287 g (SD=569) vs. 2950 g (SD=657); p<0.001] and mean gestational age [38.9 weeks (SD=1.7) vs. 38.0 weeks (SD=3.3); p=0.014] were significantly greater in the nicotine group. In a UK study (48), 1,050 pregnant smokers were randomly assigned to nicotine patch or placebo for 8 weeks, combined with behavioral counseling. Although the quit rate was higher at 1 month in the NRT group (21.3% vs. 11.7% for placebo), the rate of abstinence from the quit date until delivery did not differ significantly (9.4% for NRT and 7.6% for placebo). Importantly, however, adherence was very low. Thus, NRT does not enhance quit rates in pregnant women, possibly due to the higher rate of metabolism (i.e., inactivation) of nicotine in pregnancy and poor medication adherence in the studies.

Rationale for the Choice of Bupropion for Smoking Cessation During Pregnancy: To date, there are no published studies of bupropion SR for smoking cessation during pregnancy (49). There are several reasons to evaluate bupropion in the treatment of pregnant smokers. First, pregnancy increases the rate of nicotine metabolism (13), which diminishes

responsiveness to behavioral interventions and NRT (14, 15). Bupropion, by contrast, is efficacious for smoking cessation in fast metabolizers of nicotine (15). Second, although precise statistics are not yet available on the frequency with which bupropion is prescribed to pregnant women, it was the fourth most commonly prescribed antidepressant in pregnancy in 2007 (16). Moreover, bupropion in combination with cognitive behavioral therapy appears to promote greater smoking cessation rates and a longer time to relapse than placebo among women with smoking-related weight concerns (50), a potential contributing factor to smoking and relapse in postpartum smokers, including lower SES women (51). Further, depressive symptoms are common in pregnant women and are linked to continued smoking and data suggest that depressed smokers may respond better to bupropion than non-depressed smokers (52). Finally, bupropion appears to be safer than NRT for use in pregnancy. De Long et al. (53) examined the effect of fetal and neonatal exposure to bupropion on postnatal metabolic and reproductive outcomes in rats. In contrast to fetal exposure to nicotine (54), exposure to bupropion did not adversely affect metabolic outcomes or the fertility of the female offspring. Lastly, a small, preliminary study (55) showed that bupropion reduced CPD and improved mood among pregnant smokers more than citalopram/escitalopram.

In summary, behavioral interventions for smoking cessation in pregnant women are of limited efficacy, failing to adequately address several factors that are particularly relevant to smoking in this population (e.g., depression, rate of nicotine metabolism). Of the first-line medications, NRT has shown limited efficacy in pregnant smokers and in animal models of fetal exposure is associated with a number of potential adverse effects on offspring. Although varenicline is efficacious in non-pregnant smokers, there is an absence of safety data on its use in pregnancy. Bupropion is efficacious in non-pregnant smokers, is less likely to cause adverse fetal effects than nicotine, and is efficacious in fast metabolizers of nicotine and smokers with depressive symptoms and weight concerns (all factors that are common during pregnancy). Thus, we propose to conduct the first adequately powered RCT of bupropion to treat ND in women who continue to smoke during the second trimester of pregnancy.

Mediators and Moderators of Bupropion Response

Depressive Symptoms and Craving as Mediators of Bupropion's Therapeutic Effects: Pregnant smokers who are depressed are less likely to quit smoking than those who are not (28). In pregnant minority women, even mild depression nearly doubled the risk of continued smoking (56). Thus, we expect that, given bupropion's well-established antidepressant effects (57, 58), its efficacy as a treatment for ND will be mediated by reductions in depressive symptoms. Likewise, several symptoms that are present in pregnant smokers before quitting smoking (e.g., irritability, anxiety, difficulty concentrating, insomnia, restlessness, increased appetite, depressed mood, drowsiness) are similar to those that occur commonly during nicotine withdrawal (59). Compounded by nicotine withdrawal, these symptoms may make it more difficult for pregnant women to quit smoking (34). Because bupropion mitigates craving associated with nicotine abstinence, we expect that its efficacy in treating ND in pregnant women will also be mediated by a reduction in craving.

Metabolic, Genetic, and Social/Behavioral Moderators of Bupropion's Efficacy.

i. The rate of nicotine metabolism [i.e., the nicotine metabolic ratio (NMR)] is largely heritable (60-63) and several functional polymorphisms in the *CYP2A6* gene that affect enzyme activity have been characterized by Dr. Tyndale, a consultant to this project (64-65). However, as-yet-unidentified variants in *CYP2A6* also account for heritability in nicotine clearance (63), the rate of which is also influenced by age, sex, hormonal factors, and smoking (65-66). A genetically informed biomarker, the NMR, is based on the measurement of two long-lasting nicotine metabolites and can overcome these genotype limitations. The NMR reflects *CYP2A6* activity and the influence of other genetic and environmental influence on nicotine clearance *in vivo* (66-68). The NMR can be assessed non-invasively (e.g., from saliva, urine, or plasma)

without additional drug administration, using metabolite levels from nicotine derived from the smokers' usual cigarettes. Results are highly reproducible and independent of time since last cigarette (67). Lastly, the NMR is strongly correlated with nicotine clearance (r=.70-.95), and *CYP2A6* genotypes, in smokers of European (68-71) and African ancestry (64, 72). Importantly, NMR has been associated with smoking cessation and response to therapy in independent clinical trials (73). Smokers characterized as slow metabolizers of nicotine (the lowest quartile of the NMR) have significantly higher quit rates on NRT than faster metabolizers (higher three quartiles of the NMR) (70, 74); the same is true in African American smokers (72). In an RCT of bupropion, slow metabolizers had high quit rates on placebo, which were not enhanced by bupropion. In contrast, fast metabolizers showed high quit rates only with bupropion (15). Thus, we will examine NMR as a moderator of treatment response on the hypothesis that slow metabolizers will do well on either placebo/counseling alone or bupropion, while fast metabolizers will achieve little benefit from counseling alone (i.e., placebo), but will respond well to bupropion. This has implications for personalizing smoking cessation treatment in pregnant women.

ii. Variation in *CYP2B6*. Two studies from Dr. Tyndale's group have also shown that a variant (*CYP2B6*6*) in the gene encoding the cytochrome P450 enzyme 2B6 (which metabolizes bupropion to its major active metabolite, hydroxybupropion) moderated bupropion response. First, in a study of 326 Caucasian smokers (75), at the end of treatment and at 6-month follow up, carriers of the variant allele (45% of the sample) had significantly higher quit rates than placebo-treated subjects (32.5% vs. 14.3 and 31.2% vs. 12.9%, respectively). In the group with no variant alleles, bupropion treatment was no better than placebo in promoting abstinence. Second, in a 7-week treatment trial in 540 African-American light smokers (<11 CPD), 42.9% of bupropion-treated subjects were not adherent to treatment (20). In the 154 treatment-adherent bupropion subjects, higher hydroxybupropion (but not bupropion) concentrations resulted in higher rates of smoking cessation after 3, 7, and 26 weeks of treatment (ORs = 2.82, 2.96, and 2.37, respectively). Using alleles that have been shown to encode a reduced-function enzyme, Tyndale and colleagues found that the slow metabolizer group had significantly lower hydroxybupropion concentrations and both the slow metabolizer and intermediate groups had lower hydroxybupropion/bupropion ratios than faster metabolizers. Because 16% of African Americans and 6% of Caucasians are slow metabolizers, with the proportion of intermediate metabolizers in these groups being 48% and 38%, respectively, the potential for variation in *CYP2B6* to moderate treatment response is substantial. However, because of other influences on bupropion and hydroxybupropion concentrations (e.g., concomitant medications, hormone status, and bupropion adherence), there are inconsistent findings on the impact of *CYP2B6* variation on smoking cessation. In the present study, we will measure *CYP2B6* genotype, bupropion and hydroxybupropion concentrations, medication adherence, and enzymatic activity and the impact of these on the likelihood of smoking cessation (and risk of AEs).

iii. Smoking-related weight concerns and body image influence smoking initiation, cessation and relapse by female smokers (76) and may be of particular concern during pregnancy and the postpartum period, when women's focus on weight gain and weight loss are heightened (51, 77, 78). Pregnant women with greater weight concerns are more likely to continue smoking as a maladaptive weight control strategy, report greater appetite and weight gain as nicotine withdrawal symptoms, have lower confidence in quitting in the face of weight gain, and are less likely to quit smoking during pregnancy (77-79). Smoking-related weight concerns affect women across populations, including women in minority and low income communities, and may be related to broader patterns of body image preoccupation (50, 51, 79-81). Bupropion can offset the increased appetite associated with nicotine withdrawal (82). It could also reduce the adverse influence of weight concerns on quit rates, making such concerns an important potential moderator of response to the medication.

iv. Effects of other smokers in the home. General and cessation-specific social supports are important in promoting smoking cessation and preventing relapse in women smokers. Despite support, the presence of other smokers in the home can undermine efforts to change smoking behavior (83-86). Smoking mothers in a Healthy Start program that included a smoking cessation intervention were more likely to quit smoking and maintain abstinence if they did not have other smokers living at home (84). The negative influence of other smokers in the home on women's abstinence during pregnancy has also been seen (83), warranting an examination of the potential moderating effects of such circumstances on smoking cessation with bupropion.

Text Messaging to Enhance Adherence with Bupropion Treatment: Poor treatment adherence in smoking cessation RCTs is a key factor limiting treatment effects (87). In 2012, 2.27 trillion text messages were sent in the US (http://www.ctia.org/advocacy/research/index.cfm/aid/10323), providing a novel method to communicate health messages, including sending medical appointment reminders (88-90), providing medical test results (91), monitoring patients' AEs (92), and enhancing medication adherence (22, 23, 88, 93, 94).

Women often report that during pregnancy they seek pregnancy-related information on the Internet (95). Of particular interest to mothers are websites that present information on fetal development with content that is individually tailored to their due date or stage of pregnancy (95-98). Combining medication reminders with daily pregnancy-related topics may be particularly useful to enhance adherence because women: a) will identify with the information; b) find it engaging and personalized; and c) find that it serves both a reminder and an information function (99). In a survey of pregnant women conducted at public hospitals and health centers, 96% reported that they would like to receive text messages with information regarding prenatal care, health of the fetus, and other pregnancy educational information (100). Thus, we will utilize a personalized text-messaging system with high relevance for pregnant women to promote medication adherence.

To allow all participants to receive text messages, we will offer them cell phones with unlimited domestic talk and text for up to 32 weeks of study participation. The phones will also allow study staff to more readily contact participants and to complete the phone counseling visits. The phones will not have a data plan nor will they allow international calls or text. Participants will have the option to refuse the phone. Participants will not be responsible for the cost of lost or stolen phones. We will replace a lost or stolen phone once during the study.

Significance: The aims proposed here may increase scientific knowledge and improve clinical practice in an area with enormous public health implications by improving the outcome of pregnancies in women who smoke while pregnant. This study will be the first adequately powered RCT to examine both the efficacy and safety of bupropion for ND treatment in this subgroup of smokers. Moreover, the study will provide important information on mediators and moderators of bupropion's efficacy and demonstrate the use of a novel text-messaging system to promote treatment adherence in this population.

1.2. Investigational Agent

Bupropion is an aminoketone antidepressant with an additional indication for smoking cessation. It is chemically unrelated to other known antidepressants including tricyclics, tetracyclics, or selective serotonin re-uptake inhibitors. Bupropion weakly inhibits the neuronal uptake of norepinephrine and dopamine, but does not inhibit monoamine oxidase or serotonin reuptake. Pharmacologic activity is postulated to be mediated by noradrenergic and/or dopaminergic mechanisms. The mean elimination half-life is approximately 21 hours, and steady-state is reached within 8 days. These and other pharmacokinetic parameters in cigarette smokers did not differ from those in non-smokers. For smoking cessation, the usual dose of bupropion is 150 mg twice daily, please see attached Investigator's Brochure with medication Package Insert).

1.3 Preclinical Data

In animal studies, bupropion had pharmacologic activity similar to psychostimulants, eliciting mild stereotyped behaviors and an increased rate of response to several schedule-controlled behavior paradigms in rodents. In positive reinforcement studies, primates self-administered bupropion. In response to bupropion, rats displayed amphetamine- and cocaine-like discriminative stimulus effects.

Bupropion administered orally to rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively, showed no clear evidence of teratogenic activity. A slightly increased incidence of fetal malformations and skeletal variations were observed in rabbits. Decreased fetal weights were seen at doses of 50 mg/kg and greater. In another study, rats administered bupropion at oral doses of up to 300 mg/kg/day throughout pregnancy and lactation produced offspring showing no apparent adverse developmental effects (Zyban Package Insert).

1.4. Clinical Data to Date

No placebo-controlled trial of bupropion has been conducted in pregnant women to treat either depression or promote smoking cessation. Bupropion is classified as FDA Pregnancy Category C, meaning that although animal studies have shown an adverse effect on the fetus, there are no well-controlled studies in humans and the potential benefits of use during pregnancy may outweigh the risks.

One retrospective study examined 7,005 antidepressant-exposed pregnancies in a managed-care database. The study showed no greater risk for congenital malformations among the 1,213 bupropion-exposed first-trimester pregnancies than for other first-trimester antidepressant exposures or to bupropion use during the second or third trimesters (Zyban Package Insert). Bupropion was the fourth most commonly prescribed antidepressant in pregnancy in 2007 (16).

1.5 Dose Rationale and Risk/Benefits

To date, there are no published placebo-controlled studies of bupropion SR for smoking cessation during pregnancy (49). There are several reasons to evaluate bupropion in the treatment of pregnant smokers. First, pregnancy increases the rate of nicotine metabolism (13), which diminishes responsiveness to behavioral interventions and NRT (14, 15). Bupropion, by contrast, is efficacious for smoking cessation in fast metabolizers of nicotine (15). Second, although precise statistics are not yet available on the frequency with which bupropion is prescribed to pregnant women, it was the fourth most commonly prescribed antidepressant in pregnancy in 2007 (16). Moreover, bupropion in combination with cognitive behavioral therapy appears to promote greater smoking cessation rates and a longer time to relapse than placebo among women with smoking-related weight concerns (50), a potential contributing factor to smoking and relapse in postpartum smokers, including lower SES women (51). Further, depressive symptoms are common in pregnant women and are linked to continued smoking and data suggest that depressed smokers may respond better to bupropion than non-depressed smokers (52). Finally, bupropion appears to be safer than NRT for use in pregnancy. De Long et al. (53) examined the effect of fetal and neonatal exposure to bupropion on postnatal metabolic and reproductive outcomes in rats. In contrast to fetal exposure to nicotine (54), exposure to bupropion did not adversely affect metabolic outcomes or the fertility of the female offspring. Lastly, a small, preliminary study (55) showed that bupropion reduced CPD and improved mood among pregnant smokers more than citalopram/escitalopram.
Behavioral interventions for smoking cessation in pregnant women are of limited efficacy, failing to adequately address several factors that are particularly relevant to smoking in this population (e.g., depression, rate of nicotine metabolism). Of the first-line medications, NRT has shown limited efficacy in pregnant smokers and in animal models of fetal exposure show a number of

associated potential adverse effects on offspring. Although varenicline is efficacious in non-pregnant smokers, there are no safety data on its use in pregnancy. Bupropion is efficacious in non-pregnant smokers, is less likely to cause adverse fetal effects than nicotine, and is efficacious in fast metabolizers of nicotine and smokers with depressive symptoms and weight concerns (all factors that are common during pregnancy). Thus, we propose to conduct the first adequately powered RCT of bupropion to treat ND in women who continue to smoke during the second trimester of pregnancy.

The choice of dosage is based on the widely used dosage for smoking cessation, which is initiated at 150 mg/day with a subsequent increase to 300 mg/day (150 mg twice daily).

Potential Risks
The most common adverse events associated with bupropion when used for smoking cessation are dry mouth (11%), insomnia (31%) and dizziness (8%).

Frequent adverse reactions (occurring in at least 1% of patients) include rhinitis, neck pain, allergic reaction, hot flashes, hypertension, increased appetite, anorexia, constipation, arthralgia, myalgia, tremor, somnolence, thinking abnormality, bronchitis, pruritis, rash, dry skin, urticaria, taste perversion, asthenia, fever, headache, dyspepsia, vomiting, agitation, depression, irritability sweating, blurred vision or diplopia, and urinary frequency (Zyban Package Insert).

Infrequent adverse reactions (occurring in less than 1% but greater than 0.1% of patients) include: chills, inguinal hernia, photosensitivity, flushing, migraine, postural hypotension, stroke, tachycardia, vasodilation, abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, jaundice, stomatitis, ecchymosis, edema and peripheral edema, leg cramps and twitching, abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, parkinsonism, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo, accommodation abnormality and dry eye, polyuria, and urinary urgency (Zyban Package Insert).

Rare adverse reactions (occurring in less than 0.1% of patients) include: malaise, syncope, amnesia, ataxia, derealization, hypomania, and bronchospasm (Zyban Package Insert).

Bupropion is contraindicated in patients with a history of seizure disorder or in patients with a current or prior diagnosis of bulimia or anorexia, because of a higher incidence of seizures in these individuals when treated with bupropion.

Patients taking bupropion for smoking cessation have experienced mood changes, including depression or mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

Abuse potential: Bupropion is not likely to be reinforcing to users of stimulants, including amphetamines. Abuse of bupropion by inhalation or injection of crushed tablets have been reported, resulting in seizures and/or death.

The risk of bupropion for smoking cessation in pregnant women has not been adequately evaluated. There is a risk that bupropion could adversely affect the developing fetus.

Potential Benefits
Several medications are FDA approved for smoking cessation in non-pregnant smokers.

Nicotine replacement therapies (NRTs) partially replace the nicotine usually derived from smoking, relieving craving and other withdrawal symptoms (39, 40). The odds ratio (OR) of abstinence with NRTs compared to placebo varies from 1.5 for the nicotine gum to 2.3 for the nasal spray (12). Bupropion has an OR of 2.1 for smoking cessation (12) and has been shown to reduce depressive symptoms in smokers (42), particularly smokers with high baseline depression (52). Varenicline, an $\alpha 4\beta 2$ nicotinic receptor partial agonist (44), has an OR of 3.1 in promoting smoking cessation (12). However, there are no safety data on the use of varenicline for pregnant smokers. As discussed below, bupropion may be especially efficacious for smoking cessation in pregnant women.

Studies of NRT for Smoking Cessation during Pregnancy

In an effectiveness study (45), pregnant smokers received cognitive-behavioral therapy (CBT) and were randomly assigned to receive a choice of NRT (gum, patch, or lozenge) or no medication. Although the quit rate in the NRT group was approximately double that of the comparison group, the study was stopped because the NRT group had twice the serious adverse event (SAE) rate of the no-medication group. After adjusting for a history of preterm delivery, which was the most common SAE, the difference in SAE rate between groups was not statistically significant (p=0.09). Three efficacy studies of NRT have been conducted in pregnant smokers (46-48). In a Danish study (46), all women received counseling and either 6 weeks of a nicotine patch or placebo. At the end of pregnancy, neither quit rates nor mean CPD differed by group. However, patch compliance was poor (i.e., the average use being only 2 weeks). In a US study (47), 194 pregnant smokers were randomly assigned to receive treatment with 2 mg gum or placebo combined with individual behavioral counseling. Smoking cessation rates were non-significantly higher in the NRT group. Importantly, despite limited adherence to NRT, it produced a greater reduction in CPD and cotinine concentrations than placebo and was associated with better treatment retention. Mean (SD) birth weight [3287 g (SD=569) vs. 2950 g (SD=657); p<0.001] and mean gestational age [38.9 weeks (SD=1.7) vs. 38.0 weeks (SD=3.3); p=0.014] were significantly greater in the nicotine group. In a UK study (48), 1,050 pregnant smokers were randomly assigned to nicotine patch or placebo for 8 weeks, combined with behavioral counseling. Although the quit rate was higher at 1 month in the NRT group (21.3% vs. 11.7% for placebo), the rate of abstinence from the quit date until delivery did not differ significantly (9.4% for NRT and 7.6% for placebo). Importantly, however, adherence was very low. Thus, NRT does not enhance quit rates in pregnant women, possibly due to the higher rate of metabolism (i.e., inactivation) of nicotine in pregnancy and poor medication adherence in the studies.

Risk-Benefit Ratio

As described above, there are several reasons to evaluate bupropion in the treatment of pregnant smokers, who along with their offspring are at substantial risk from smoking. Despite an absence of safety data for bupropion use in pregnancy, preclinical data show that, particularly during the second trimester of pregnancy, the medication has not been associated with substantial risk of adverse effects on the fetus. As a consequence, obstetricians often choose bupropion to treat depression in pregnant patients. Based on the substantial potential risk and limited risk of adverse effects, the risk-benefit ratio for the proposed study appears to be positive.

2. Study Objectives

Specific Aim 1: Conduct a 10-week placebo-controlled trial of bupropion 300 mg/day in 360 pregnant smokers who are at 13–26 weeks gestation. We will monitor smoking behavior and adverse effects (AEs) of the medication during a 10-week treatment period, with follow up for

the remainder of the pregnancy (measuring length of gestation, rate of pregnancy complications, and birth outcomes). We will also provide two booster counseling sessions at weeks 2 and 6 postpartum and a final research evaluation at 24 weeks post-TQD. We will use text messages to send pregnancy-relevant information and medication-adherence cues based on their demonstrated ability to improve adherence in various populations (e.g., 22, 23). We hypothesize that:

H1: Bupropion-treated women will have a greater rate of biochemically confirmed cigarette abstinence than placebo-treated women.

H2: There will be no significant differences between treatment arms in the frequency of severe treatment-related AEs.

H3: Bupropion treatment will result in a higher birth weight than placebo.

Specific Aim 2: Assess changes in depression symptoms and craving as mediators of bupropion's effect on quit rates.

Exploratory Aim: Explore genetic, metabolic, and social/behavioral moderators of the efficacy of bupropion on cigarette abstinence and safety. To generate new hypotheses, we will explore whether the risk of AEs and the efficacy of bupropion treatment (vs. placebo) is moderated by: 1) the rate of nicotine metabolism (i.e., nicotine metabolite ratio (NMR)] and variation in *CYP2A6*; 2) variation in *CYP2B6* and plasma concentrations of bupropion and hydroxybupropion; and 3) variation in social/behavioral variables, including weight concerns, body image, and the presence of other smokers in the home.

3. Study Design

3.1 General Design

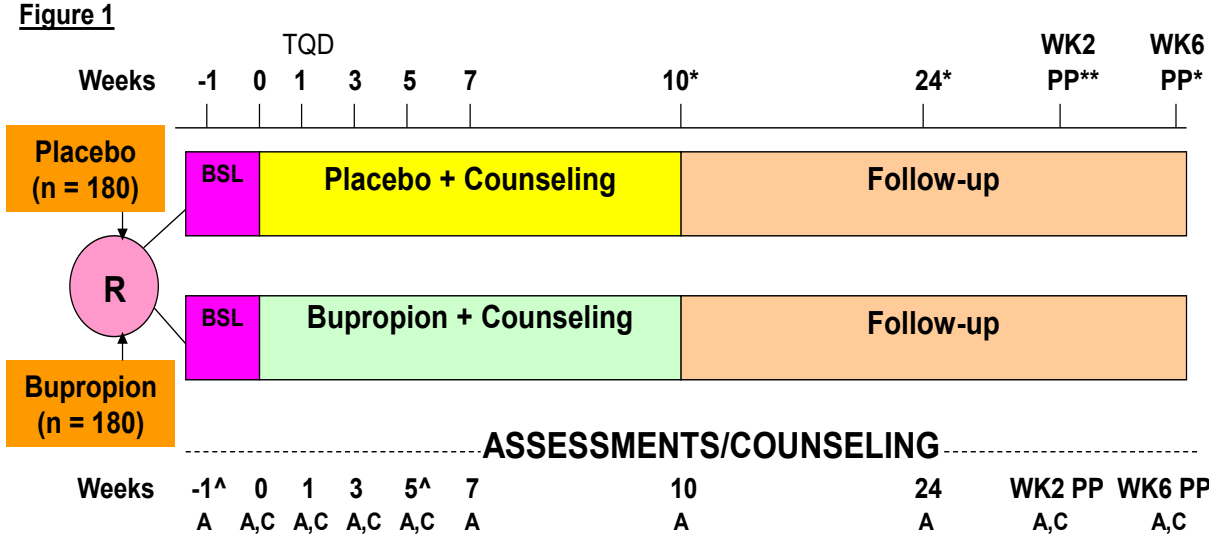
Phase II Study - This is a phase II, prospective, placebo-controlled RCT of the efficacy and safety of bupropion in combination with behavioral counseling for smoking cessation during pregnancy (see Fig. 1). Pregnant smokers (N=360) will receive bupropion or placebo treatment for 10 weeks, under strict double-blind conditions, with 3 post-treatment follow-up sessions: 2 and 6 weeks postpartum (with counseling to prevent relapse or encourage a repeat quit attempt) and monitoring of the persistence of treatment effects at 24 weeks post-TQD.

Study Duration – The duration of the treatment will be 10 weeks with 3 post-treatment follow-up visits: 2 weeks and 6 weeks postpartum and 24 weeks post-TQD. Birth outcomes will be obtained from labor and delivery records (permission for which will be included in the informed consent form). The entire study will run for approximately 54 months from the first participant enrolled to the last participant assessed at 24 weeks post TQD.

3.2 Primary Study Endpoints

- Primary smoking status will be assessed using the Timeline Follow-back method (165) and by using carbon monoxide (CO) concentration to biochemically verify the self-report. Participants will be considered to be abstinent if they self-report abstinence (not even a puff

Figure 1



BSL = Baseline (and Intake Session and Randomization); A = Assessment; C = Counseling; TQD = Target Quit Day; ^ Corresponds to blood draw for NMR (week -1) and for assessment of bupropion and bupropion metabolites to assess adherence; * Corresponds to End-of-Treatment and 6-months post-TQD and primary outcomes; ** Two additional brief counseling/assessment sessions will be provided at 2- and 6-weeks postpartum (PP).

of a cigarette) for ≥7 days prior to the assessment after 10 weeks of treatment and at 24 weeks post-TQD and have a CO ≤10 ppm at that time (166-167). As per convention, participants are assumed to be smoking if they self-report to be smoking at the time point, cannot be reached to provide data at the time point, fail to provide a breath sample at the time point, or provide a breath sample at the time point that has a CO concentration >10 ppm (166).

- For adverse effects, our primary outcome will be the frequency of moderate or severe side effects from a checklist of bupropion-related side effects (derived from completed bupropion studies), as well as those elicited with open-ended questions, through regular obstetrics visits, and assessments triggered by any pregnancy-related complication. Adverse effects will be systematically assessed by study personnel at 5 time points over the course of the 10-week study and can trigger dose reductions or suspension of medication.

- Birth outcomes obtained from labor and delivery records (permission for which will be included in the informed consent form) will include gestational age, overall and spontaneous preterm birth (i.e., at less than 37 weeks), infant birth weight, whether small for gestational age (i.e., <10th percentile birth weight for gestational age as determined by the Alexander curve), head circumference, Apgar scores, and NICU admissions. Obstetric complications will include type of delivery and delivery and postpartum complications.

3.3 Secondary Study Endpoints

Secondary smoking cessation outcomes include: smoking rate after 10 weeks of treatment and at 24 weeks post-TQD for non-abstainers, prolonged abstinence to weeks 10 and 24

(defined below), continuous abstinence at weeks 10 and 24 (defined below), time to 7-day relapse (no grace period), and lapse and recovery events.

3.4 Safety Endpoints

Participants with severe psychological symptoms (e.g., suicidal thoughts), experiencing a serious adverse event that the Principal Investigator believes to be related to study drug and a potential threat to the health and safety of the participant or fetus will be withdrawn from the study (see section 8.1).

4. Participant Selection and Withdrawal

4.1. Inclusion Criteria

1. Currently smoking on average 3 or more cigarettes per day for the preceding 7 days with a breath CO of at least 5 ppm and wants to quit smoking
2. Pregnant at 13-26 weeks gestation (to maximize safety and the likelihood of receiving 10 weeks of treatment)
3. ≥18 years of age
4. Able to speak and read English at a 6th grade level or higher, using the Slosson Oral Reading Test (SORT)
5. Committed to remaining in the geographic area for at least 3 months postpartum
6. Able to sign written informed consent and commit to completing the procedures involved in the study.
7. Methadone or buprenorphine-maintained women must be in methadone or buprenorphine treatment for a minimum of 2 weeks prior to entering the study. Their 2 most recent urine drug screens, consecutive and administered at least one week apart, must both be positive for methadone or buprenorphine and negative for drugs of abuse other than cannabis. Participants who screen positive for other drugs at either time point will not be enrolled in the study until they meet this criterion.

4.2. Exclusion Criteria

1. During the last 90 days from screening visit, meets any criteria for a DSM-IV diagnosis of drug or alcohol dependence—excluding tobacco or cannabis dependence and, for methadone or buprenorphine maintenance patients, opioid dependence—**AND** either evidences ongoing use of illicit drugs other than cannabis or continues to abuse or misuse prescription drugs such as CNS stimulants.
2. Pregnant with triplets or higher order multiples
3. Has an unstable psychiatric disorder (i.e., suicide risk moderate or severe, as reflected by a score of ≥9 on the MINI Section B (Suicidality) or a suicide attempt during the preceding year, psychiatric hospitalization within the last 3 months; current psychotic disorder based on the MINI)
4. Current or past Bipolar Disorder as determined by a study psychiatrist or psychologist based on assessment with the MINI, relevant information from the medical record and, when warranted, direct clinical evaluation.
5. Current, regular use of psychotropic medication, inhibitors of CYP2B6 (e.g., ticlopidine, clopidogrel), inducers of CYP2B6 (e.g., ritonavir, lopinavir, efavirenz), anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin), beta-blockers (e.g., metoprolol), Type 1C antiarrhythmics (e.g., propafenone and flecainide), drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen), drugs that lower seizure

threshold (e.g., antipsychotics, tricyclic antidepressants, theophylline, or systemic corticosteroids), levodopa or amantadine

6. Current unstable medical problems or potential inability to tolerate study treatment [e.g., threatened abortion: current persistent hyperemesis gravidarum (HEG) requiring intravenous fluids (to be rescreened when HEG is stabilized/resolved and no electrolyte abnormalities are evident); hypertension with evidence of end organ dysfunction or on more than 2 medications at the start of the pregnancy]; arteriovenous malformation; AIDS; laboratory evidence of hepatic impairment (e.g. viral hepatitis with serum transaminase levels more than twice the upper limit of normal) ; renal impairment (e.g., elevated creatinine or creatinine clearance <75cc/hr), metabolic disorders (e.g., hypoglycemia, hyponatremia) or end organ damage from any chronic medical condition (e.g. abnormal pulmonary function tests), glaucoma, or other significant medical problems that in the opinion of a study obstetrician makes the risk of study participation unacceptable.
7. Known major fetal congenital malformation—as determined by the study obstetrician—diagnosed prior to study randomization
8. History of seizure disorder
9. Current use of a smoking cessation medication in addition to the study medication, such as nicotine replacement therapy
10. Current or history of bulimia or anorexia nervosa
11. Current use of tobacco products other than cigarettes (e.g., E-cigarettes)
12. Current clinically significantly abnormal laboratory evaluations that are not adequately controlled by standard of care treatment.
13. History of severe head injury (i.e., with loss of consciousness)
14. Any medical condition or concomitant medication that could compromise subject safety or treatment, as determined by the Principal Investigator and/or Study Physician.
15. Inability to provide informed consent or judged by the Principal Investigator and/or Study Physician to be an unsuitable candidate for a clinical drug trial.

4.3. Participant Recruitment and Screening

All sites will have a senior clinician to oversee the integration of the trial into clinical practice. Approval from the City of Philadelphia Institutional Review Board and the Health Commissioner's Office will be obtained given the involvement of Philadelphia Department of Public Health data, staff, and clients at the Jefferson MATER site, where methadone-maintained pregnant smokers will be enrolled. Buprenorphine-treated subjects will be recruited from the "Mothers MATTER" program at the Dickens clinic and from the Jefferson MATER site. As in our previous successful clinical trials (e.g., 14, 47, 52), we will use experienced and trained research staff to identify and screen potentially eligible participants in the clinics. Recruitment sites will also be provided with IRB-approved materials designed to raise awareness of the study, including posters and brochures to be displayed prominently in all clinic areas. We will also encourage referrals from clinicians in the surrounding areas at each site, and will recruit through newspapers, maternity magazines and social media. Interested and potentially eligible participants will be scheduled for an intake session (week -1) to determine eligibility. For details on Screening, see 6.2 Informed Consent and Screening Visit below.

4.4. Early Withdrawal of Participants

4.4.1. When and How to Withdraw Participants

Participants with severe psychological symptoms (e.g., suicidal thoughts), those who fail to adhere to protocol requirements, and those who withdraw consent will be withdrawn from the

study and if applicable, referred for appropriate clinical care. Any participant experiencing a serious adverse event that the Principal Investigator believes to be related to study drug and a potential threat to the health and safety of the participant or fetus will be withdrawn from the study (see section 8.1).

4.4.2. Data Collection and Follow-up for Withdrawn Participants

We will make a strong effort (via phone calls and alternative contact information) to obtain follow-up information on all participants who are prematurely withdrawn from the project.

5. Study Drug

Bupropion is an antidepressant medication for oral administration approved in the United States for the treatment of Major Depressive Disorder, Seasonal Affective Disorder and Smoking Cessation in adults. For more detailed information, see section 1.2 (Investigational Agent).

5.1. Description

Bupropion for this study is supplied as commercial SR 150mg tablets. The placebo will be supplied as over-the-counter calcium carbonate 648mg tablets which are nearly identical in size, shape and color to the active bupropion product.

5.2. Treatment Regimen

Participants will be randomized to receive Bupropion or placebo, to begin after completing the Baseline visit according to the regimen in Table 1 below.

5.3. Method for Assigning Participants to Treatment Groups

Participants will be randomly assigned to one of two treatment conditions: Bupropion 300 mg/day (n = 180) or placebo (n = 180). We will use small-block randomization by site (Penn or MATER) provided by Dr. Lynch, the study biostatistician. A PHQ-9 score of 10 or greater will be used to identify major depression and stratify the randomization on it. Study site (Penn or MATER) will be the second of the two stratification variables. Study staff and the Investigational Drug Service (IDS) staff will be responsible for medication randomization. The process for randomization is: 1) The research coordinator will complete a “randomization form,” which includes the variables to be entered into the randomization program and fax or email the form without protected health information to the UPenn site; 2) A designated study staff member

Table 1: Medication Dispensing Schedule

	Medication Dispensed For	**Morning Dose**	**Evening Dose**	**Total Daily Dose**
Visit A: Screening	N/A	No medication	No medication	
Visit B: Baseline	Wk 1	150 mg	No medication (for first 3 days); then 150 mg	150 mg
Visit C: Wk 1	Wk 2 through Wk 5	150 mg	150 mg	300 mg
Visit D: Wk 3	N/A	N/A	N/A	N/A
Visit E: Wk 5	Wk 6 through Wk 10	150 mg	150 mg	300 mg
Visit F: Wk 7		150 mg	150 mg	300 mg
Visit G: Wk 10	Endpoint	No medication	No medication	N/A

Visit H: Wk 24 Post-TQD	N/A	No medication	No medication	N/A
Visit I: 2 wk postpartum	N/A	No medication	No medication	N/A
Visit J: 6 wk postpartum	N/A	No medication	No medication	N/A

at the UPenn site will enter the variables into the randomization program, which will assign a randomization group to the participant; 3) the designated study staff member will fax the participant's randomization group to IDS, which will assign a kit number to the participant and fax the kit assignment to the research coordinator; 4) the research nurse or physician will dispense medication to the participant and complete and sign the IDS prescription form included in the starter kit; 5) The research coordinator will fax the completed form to IDS. The medication will be dispensed using the above dosing schedule. To maintain double-blind conditions, study staff responsible for randomization will not be involved in the recruitment of participants, study visits, or data collection. IDS will provide each study site a supply of starter kits to use for initial study medication dispensing.

Study drug for subsequent visits will be ordered by the research coordinator using the "Research Pharmacy Schedule" form, a copy of which will be retained in the participant's research file. The study drug will be ordered at Baseline Visit B for Weeks 2-5 and Target Quit Day Visit C for Weeks 6-10. The study drug will be picked up at IDS and brought to the study visit. If the participant is unable to attend the scheduled study visit the study drug will be stored at the Treatment Research Center in the Medication Room. Study drug will be dispensed at three time points during the study: Baseline (Visit B: 1 week of medication), Target Quit Date (Visit C: 4 weeks of medication), and Week 5 (Visit E: 5 weeks of medication). The initial dispensing will be done directly by the research nurse or physician, who will ensure that the patient understands the medication regimen. Study medication will be dispensed by the research nurse, physician, or research coordinator (trained and supervised by the nurse or physician), who will assess each participant for study medication AEs, documenting and reporting them as required. Participants with severe psychological symptoms or determined to be inappropriate for the study by an investigator will be withdrawn from the study. A study nurse or physician will follow participants withdrawn completely from treatment until they are referred for appropriate clinical care. For research purposes, and with the participant's continued approval, we will collect data at all subsequent time points until the 24 weeks post-TQD visit.

5.4. Preparation and Administration of Study Drug

5.4.1 Chemistry and Manufacturing: Bupropion sustained-release 150mg tablets will be purchased commercially, as round white tablets with only an imprint. An over- the-counter calcium supplement in tablet form, with similar shape and color, will be used as the 'placebo' for bupropion tablets in this clinical trial. Medication will be prepared at the University of Pennsylvania, Investigational Drug Service, 3600 Spruce Street, Ground floor Maloney Building, Philadelphia, PA 19104.

5.4.2 General Method of Preparation and Packaging: The Investigational Drug Service will purchase Bupropion sustained-release 150mg tablets (made by Watson Laboratories) from a pharmaceutical wholesaler. These tablets were selected because they are round, white and have an imprint on only one side of the tablet.

The tablets will be used without alteration. For dispensing to study participants, they will be packaged in blister cards with the imprint facing the foil, so that members of the research team cannot see the imprint side of the tablet.

5.4.3 Drug Components and Drug Product: The finished drug product will consist of the following components:

a. Bupropion sustained release 150mg tablet. Source: Watson Laboratories (NDC# 00591-0839-XX)

b. Placebo Product: For the purpose of conducting this clinical trial, an over the counter supplement with similar appearance to the active bupropion tablet, will be used as the placebo control. The tablet will be used unaltered. For purposes of maintaining the study blind, tablets will be dispensed in a blister card, with the imprint facing the foil, so that members of the research team cannot see the imprint side of the tablet. The finished drug product will consist of the following components: Calcium Carbonate, 648mg. Source: Major Pharmaceuticals (NDC# 00536-3414-10)

c. Labeling: The following label will be placed on the blister card at time of dispensing to a study participant:

Caution: New Drug Limited by Federal (USA) Law to Investigational Use Only	University of Pennsylvania – Investigational Drug Service 3600 Spruce Street – Ground Maloney – Philadelphia PA 19104 215-349-8817 RX # XXXXXXXXX Dr. _____ Patient: XXXXXX (######) Date: _____ **TAKE ONE (1) TABLET BY MOUTH EACH DAY AS DIRECTED.** IND# ###### Study Period: ____ **BUPROPION SR 150 MG OR PLACEBO TABLETS #9** Study ####### Refills: 0	*INVESTIGATIONAL* DRUG **[BARCODE HERE]** Rx# XXXXXXXXX

d. Environmental Analysis Requirements; Given the planned use of the investigational agent in this study, we believe an environmental analysis is not required.

5.4.4 Provide study medication to study sites IDS will provide study medication for the MATER, Jefferson and Penn study sites. Treatment will last for 10 weeks and medication will be dispensed in 4 increments: At baseline, participants will receive medication for week 1; at week 1, they will receive medication for weeks 2 through 5; and at week 5 for weeks 6 through 10. IDS will provide each study site a supply of starter kits to use for initial study medication dispensing. Study medication will be stored at room temperature (59-86º F) in a locked drawer in the TRC study medication storage room. The room is monitored daily for temperatures and has limited study staff access. The study medication will be stored until dispensed by the nurse or study coordinator for distribution to participants.

5.5 Participant Compliance Monitoring

We will conduct tablet counts at each in-person visit for all study participants. Unused amounts will be documented. Proper drug dosing will be reviewed with participants at each visit with clear instructions to take all study tablets as directed. Study coordinators at each clinical site will maintain a tracking log of all study medication ordered from IDS, dispensed to participants, returned by participants and then returned to IDS. Coordinators will return study medication blister packs and unused study medication to IDS after each participant completes the last follow-up visit.

5.6 Packaging

The Investigational Drug Service of the University (IDS) of Pennsylvania will package bulk drug on-site, containing medication in blister packaging. Medication will be dispensed in amounts as described in Study Procedures (below).

5.7 Blinding of Study Drug

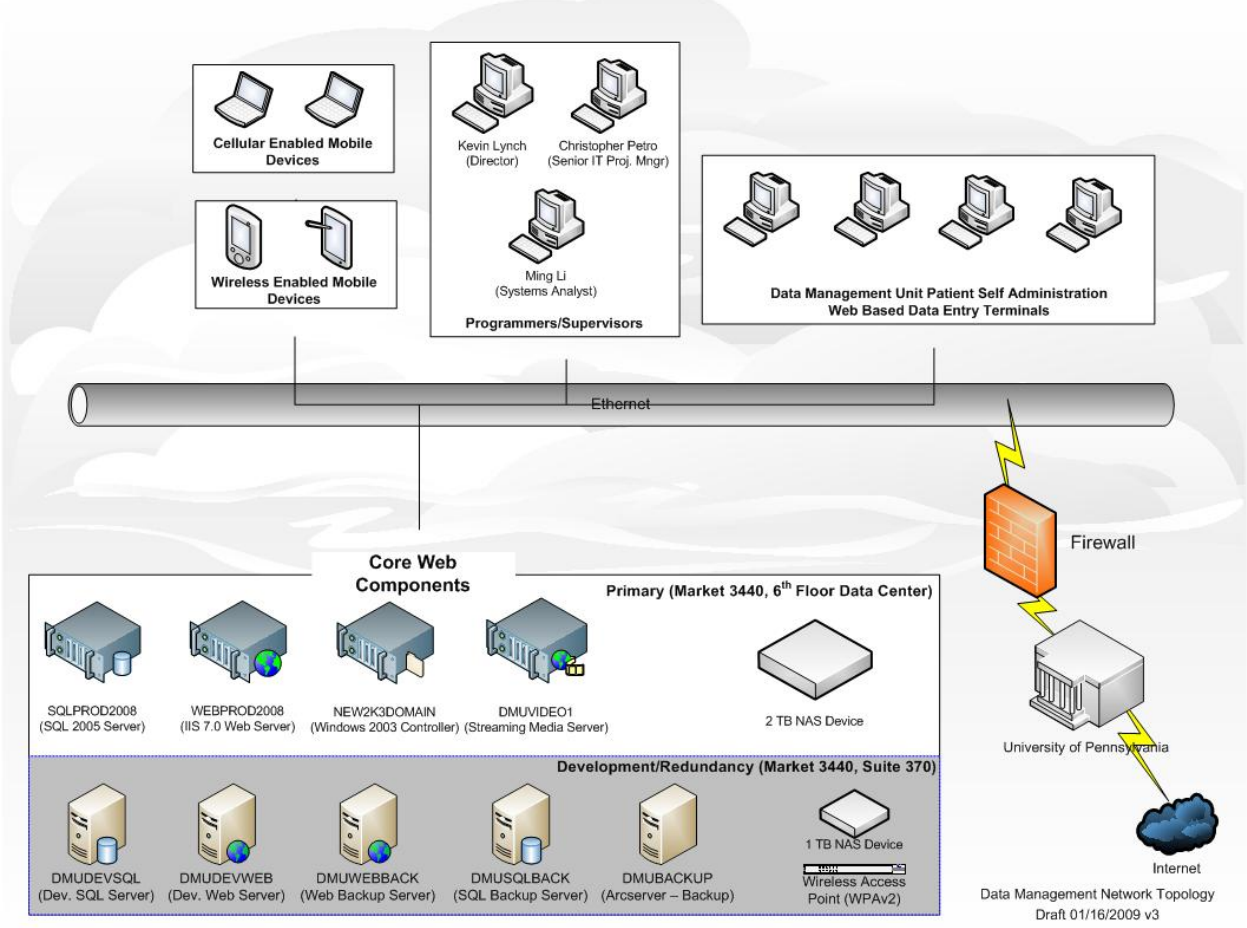
All participants and research staff will be blinded as to whether the participant is in the bupropion or placebo group until the end of the study once the decision to break the study blind is determined (after study database lock). Codes linking randomization number for each participant to actual treatment will be secured in a sealed, opaque envelope and maintained in a locked drawer in the research pharmacy and the hospital pharmacy. Research participants will be given the emergency contact number for the study during the consenting process.

See section 8.4 (Unblinding Procedures) for a description of the process for unblinding a study participant.

6. Study Procedures

6.1 Recruitment

We will distribute IRB-approved recruitment materials (i.e. brochures, post cards and posters) to recruit women who smoke and wish to quit smoking through participation in the trial. We will work with Jefferson and Penn OB clinics to access EPIC to identify pregnant smokers receiving prenatal care and, working with their obstetrician, invite them to consider study participation. We will ask clinicians for permission to mail IRB-approved recruitment materials to their patients, who have reported recent smoking behavior and may meet study inclusion criteria based on EPIC screening. We will also advertise in media, including online classifieds such as Craigslist, newspapers (print and online), magazines, radio, and social media. We will use Facebook and Instagram to post study recruitment ads, including pictures and texts. Interested individuals can click a link that will redirect them to the recruitment landing page. The landing page will ask interested participants to fill in information—including name, phone number, pregnancy status and smoking status—to determine whether they are eligible. The landing page will be housed on a secure web server that is encrypted and password protected with different levels of user access and privileges. The web server—our Data Management Unit (DMU)—is flexible and ensures data quality and security (see appendix).



We will post and distribute recruitment material in community settings with public posting areas or other means of providing community access to materials (such as town halls, public libraries, YMCAs, health fairs). We will obtain permission at select locations before distributing or posting the approved recruitment materials (ensuring compliance with other institutions guidelines, including seeking IRB approval as needed to conduct recruitment activities). We will also encourage referrals from clinicians in the surrounding areas at each site including Penn Family Medicine. At the Jefferson site, we will recruit patients from MATER (Maternal Addiction, Treatment, Education and Research, which provides methadone maintenance treatment for pregnant women), part of the Pediatrics Department. MATER is located at 1233 Locust Street, 4th floor, Philadelphia, PA 19107, which is where recruitment will take place and treatment will be delivered. We will also recruit patients from Jefferson University Department of Obstetrics and Gynecology Associates (JOGA).We will conduct a brief in-person pre-screening questionnaire and a screening interview over the phone or in-person at the participant's obstetrics clinic to assess study eligibility criteria. At Jefferson, medical records will be reviewed for gestational age and smoking status to identify prospective participants. Prospective participants who appear to meet eligibility criteria for the study will be scheduled for an in-person Informed Consent and Screening visit. See Table 2 below for the schedule of assessments. Buprenorphine-treated women will be recruited through the Penn and Jefferson MATER sites as described above.

6.2 Visit A: Informed Consent and Screening (Approximately 60 minutes, in-person)

In a private setting, each participant will receive a description by a study staff member of the study protocol, its risks, potential benefits, and alternative treatments available. Following resolution of any questions, participants who appear to understand the nature of the study and consent will be asked to sign the study consent form. We have created two informed consent forms (ICFs), one for Penn and one for Jefferson, to address site-specific differences. An entire copy of the ICF will be given to each participant, who will be reminded that the consent expresses her willingness to participate but that the subsequent screening process will determine final eligibility. Further, she will be reminded that participation is voluntary, and at any time, she may withdraw from the study. Following the informed consent process, a research coordinator will obtain demographic information, administer a reading test (SORT), and extract information from the patient's medical record (including medical history and medications, obstetric history, blood pressure, and weight), and perform a psychiatric diagnostic interview (MINI; sections A through K) the PHQ-9 to differentiate depressed and non-depressed women for randomization, and a Timeline Follow-back smoking interview covering the preceding 30 days. We will also measure breath CO at this and every subsequent visit.

The participant will also be asked to provide locator information. Selection of follow-up locators is particularly important for the successful tracking of patients for follow-up evaluations. Study staff will select patient locators on the basis of relationship to client, duration and current status of relationship, frequency of contact with the patient, and willingness to participate. Locators are contacted when efforts to reach a patient are unsuccessful, which contributes both to maintaining patients in treatment and enhancing data collection. Participants will be asked for one or two locators.

The initial assessment in the clinic will help to exclude ineligible participants, facilitate clearance by an obstetrician for any medical condition that requires approval (e.g., mild hypertension), and ensure that the woman's gestational age is 13-26 weeks. Gestational age will be assessed for enrollment purposes based on the method used by the NICHD-sponsored Maternal-Fetal Medicine Units Network. The gestational age will be based on the projected estimated date of delivery (EDD), as determined by U/S and the last menstrual period (LMP;see below). Because the project EDD depends on information from the earliest dating U/S, <u>if no U/S has been performed previously, one will be performed to determine eligibility</u>. The EDD also requires that the first day of the LMP be determined and a judgment made as to whether or not the participant has a "sure" LMP.

- If the LMP date is uncertain, the U/S measurements obtained at the participant's first U/S will be used to determine the projected gestational age, by the standard method used at the recruitment site.
- If the date of the LMP is certain and the U/S confirms the gestational age within +/- 7 days, the LMP-derived gestational age will be used to determine the project gestational age.
- If the U/S-determined gestational age does not confirm the LMP-generated gestational age within +/- 7 days, the U/S will be used to generate the project gestational age.

Thus, all participants will be assigned a project EDD and gestational age when they are evaluated for enrollment. An U/S machine is available at each recruitment site and results will be supervised and reviewed by Dr. Srinivas (Penn) or Dr. Jason Baxter, M.D. (Jeff).

6.3 Visit B: Baseline (Pre-quit) (Approximately 90 minutes, in-person or divided between in-person and telephone sessions)

Although this session requires an in-person visit, part of the session may be completed via telephone. The session must be completed 1-30 days after completion of the screening visit. At the in-person visit, we will measure breath CO level and draw three tubes (i.e., 21 cc) of maternal blood to assess NMR and provide DNA for genotyping. Blood will be stored in a coded manner in a designated -80° freezer and shipped on dry ice to the laboratory of Dr. Rachel Tyndale at the University of Toronto approximately every four months throughout the study. Samples from both sites will be shipped from their storage location at Penn (see section 9.5) and will follow the guidelines for shipping international biological samples as required by the university.

Table 2: Study Assessments

	Visit A	**Visit B**	**Visit C**	**Visit D**	**Visit E**	**Visit F**	**Visit G**	**Visit H**	**Visit I**	**Visit J**
	Screen	**Baseline (Pre-quit)**	**Wk 1 (TQD)**	**Wk 3**	**Wk 5**	**Wk 7**	**Wk 10**	**Wk 24**	**Wk 2 PP**	**Wk 6 PP**
ICF with HIPAA	X									
Medical record review	C									
Med History Questionnaire	X									
Demographics	X									
SORT	X									
MINI[1]	X				X[2]		X[2]			
TLFB (preceding 30 days)	X									
Gestational Age	X, C									
Blood sample: DNA, NMR		X								
Breath CO*	X	X	X		X		X	X[3]		
Dispense medication		X	X		X					
Text messaging		Daily	Daily	Daily	Daily	Daily	Daily			
Assessment of AEs and medication adherence		X	X	T	X	T	X			
Weight, blood pressure	X or C	C	C	C	C	C	C			
Pulse		X	X		X		X			
ACE questionnaire		X or T								
Smoking History Questionnaire		X or T								
FTND		X or T								
BISS		X or T								
WEAQ		X or T								
PHQ-9	X	X or T	X	T	X	T	X	X	T	T
QSU		X or T	X		X		X			
MED-Q							X			
TLFB (since last visit)		X or T	X	T	X	T	X	X	T	T

Smoking cessation counseling (30 min)		X								
Smoking cessation counseling (20 min)			X							
Smoking cessation counseling (10 min)				T	X				T	T
Blood sample: [bupropion, hydroxybupropion]					X					
Birth outcome data								C		

TQD: target quit date; PP: postpartum; ICF: informed consent form; HIPAA: Health Insurance Portability and Accountability Act; Assessments: X=in-person; X^1=MINI sections A through K will be administered. X^2=Only MINI section B (Suicidality) will be administered; X^3=in-person only; T=by telephone; C=chart review; SORT: Slosson Oral Reading Test; MINI: Mini-International Neuropsychiatric Interview; TLFB: Timeline Follow-back Interview for cigarettes smoked; NMR: nicotine-metabolite ratio; [CO]: carbon monoxide concentration; AEs: adverse events FTND: Fagerstrom Test for Nicotine Dependence; BISS: Body Image State Scale; PHQ-9: Patient Health Questionnaire-9; WEAQ: Weight Efficacy After taken Quitting survey; QSU: Questionnaire of Smoking Urges; MED-Q: medication group question; *CO readings may also be at the time of delivery and at the time of the post-partum office visit

An in-person or telephone interview will be used to obtain background information for use as potential covariates and to assess the study's external validity [including smoking history (e.g., age at initiation, past use of nicotine treatments, current rate, menthol vs. regular tobacco, presence of other smokers in the home), obstetrical history to confirm and augment information obtained from review of the medical record (number of pregnancies, pregnancy outcomes), and medical and psychiatric history (with current medications extracted from the medical chart). Sessions in which the assessments are conducted by telephone, the telephone interview should be completed prior to the in-person visit.

Nicotine dependence severity will be assessed with the Fagerstrom Test for Nicotine Dependence, a validated 6-item measure (144). We will measure depression symptom score using the PHQ-9 (145) and will use a score of 10 or more to differentiate depressed and non-depressed women. This cut point will enable us to use depression as a stratification variable and potential mediator. Craving severity, which has been related to long-term cessation in cessation trials (147), will be measured with the 10-item brief Questionnaire of Smoking Urges (QSU; 146). The QSU contains 2 subscales (anticipation of reward, relief from negative affect.

Weight concerns will be measured using the Weight Efficacy After Quitting survey, a 6-item validated scale that assesses general and smoking- specific weight concerns (148). We will also use the Body Image States Scale (BISS) (149), a 6-item measure of evaluative and affective experiences of one's physical appearance. Body image may be a more potent moderator of smoking cessation treatment effects (and such concerns are particularly relevant in pregnant women). A single item in the smoking history questionnaire will assess the number of smokers in the home. The Adverse Childhood Experiences (ACE) questionnaire, a 10-item self-report measure will be administered at this time as well.

Following the assessments, participants will receive the first session of manual-based counseling from a coordinator that is trained and supervised by Dr. Schnoll. The counseling protocol is based on Public Health Service guidelines for smoking cessation treatment (12) and is intended to enhance study retention and ensure that participants in the placebo arm receive active treatment to quit smoking. The 30-minute, "pre-quit" counseling session will prepare for the target quit day (TQD). This session focuses on reviewing the participant's history and experience with quitting, beliefs about smoking and quitting, and perceived barriers to cessation. The participant will receive a one-week supply of study medication and the nurse or physician will review with the participant instructions for taking the study medication, which include instructing the participant to begin taking the medication on the following morning. Study staff will complete a baseline adverse event checklist, an open-ended evaluation of any existing symptoms using the established study checklist of adverse events, before the subject begins taking the study medication.

Upon initiation of the medication, subjects will begin to receive daily text messages describing the progress of their pregnancy and reminding them to take their medication. The text messaging will continue throughout the 10-week medication treatment period. The greatest impact of this approach has been seen with interventions that include personalized text message reminders and interactivity (105). Personal tailoring will involve: 1) flexibility in the timing of receipt of messages each day ("set time" chosen by the woman) and 2) day-by-day facts, tips, suggestions, and benchmarks appropriate to each stage of fetal development calculated using the woman's estimated date of delivery. The morning message will consist of 2 components: a "hook" text that details the fetus' development and pregnancy tips and a "prompt" text reminding the subject to take her medication at the prescribed times. We will use a database of messages consisting of SMS text and rules to determine which message to send based on gestational age, time of day, and the participant's previous replies. An example morning message is:

Your baby's heart is now developed. Remember to take your study medication with your morning and evening meals.

The evening message will ask participants whether they took their study medication as prescribed:

Did you take the study medication as prescribed today?
Reply
"1" for Yes, I took it today
"2" for No, I did not take it today

If participants do not respond to the evening message within 1 hour, a reminder message will be sent ("*Did you take your study medication as prescribed today. REPLY "1" for Yes, I took it today; "2" for No, I did not take it today*."). A maximum of three text messages will be sent in a given day.

All participants will be offered a free cell phone with unlimited talk and text for up to 32 weeks of study participation to allow them to receive the text messages, participate in phone counseling and to contact study personnel. Participants have the option to refuse the phone. They will be asked to return the phone to the study staff at the end of the study. They will be paid $20 for returning the phone. Participants will not be responsible for the cost of lost or stolen phones. We will replace a lost or stolen phone once during the study.

6.4 Visit C: Week 1 (Target Quit Day) (Approximately 45 minutes in person)

At the in-person visit, we will measure breath CO level and the participant will receive a four-week supply of study medication. The nurse or coordinator (trained and supervised by the nurse or physician) will review with the participant instructions for taking the study medication and record any AEs that the participant may have experienced. The nurse or coordinator will also collect empty medication blister packs and any unused medication. In-person or by telephone, participants will complete the PHQ-9, QSU, will be interviewed with the TLFB, and will receive a 20-minute, "quit-day" counseling session to review the initial quit attempt, identify potential reasons for relapse, and review a plan to avoid tempting situations.

6.5 Visit D: Week 3 (Approximately 25 minutes by telephone or in person)

Participants will be asked to complete the PHQ-9 and the TLFB by telephone. They will then receive a 10-minute booster counseling session that focuses on reinforcing success and reviewing the quit plan (for participants who have quit smoking) or re-establishing a quit date

and restarting the cessation process (for participants who have relapsed to smoking). The counseling schedule reflects the changing needs of the pregnant smoker during the course of pregnancy and smoking cessation (155), with more intensive help offered in the earliest phase of treatment and continued efforts to prevent relapse in the later stages.

6.6 Visit E: Week 5. (Approximately 30 minutes in-person)

At the in-person visit, we will measure breath CO level, and participants will meet with a study nurse or coordinator working under the supervision of the nurse or physician to receive a five-week supply of study medication. The nurse or coordinator will review with the participant instructions for taking the study medication and record any AEs that the participant may have experienced. The nurse or coordinator will also collect empty medication blister packs and any unused medication. Two tubes of blood (14 cc) will be drawn at this visit for shipment to Dr. Tyndale's laboratory at the University of Toronto to measure plasma concentrations of bupropion and hydroxybupropion. Participants will be asked to complete PHQ-9, QSU, and TLFB, either in person or by telephone. They will then receive a 10-minute booster counseling that focuses on reinforcing success and reviewing the quit plan (for participants who have quit smoking) or re-establishing a quit date and restarting the cessation process (for participants who have relapsed to smoking). Suicidal risk will be assessed using the MINI Suicidality section (B).

6.7 Visit F: Week 7. (Approximately 15 minutes by telephone or in person)

Participants will be asked to complete the PHQ-9 and TLFB by telephone.

6.8 Visit G: Week 10 (Endpoint). (Approximately 25 minutes in-person)

At the in-person visit, we will measure breath CO level. The nurse or coordinator (trained and supervised by the nurse or physician) will review with the participant any AEs that the participant may have experienced. The nurse or coordinator will also collect empty medication blister packs and any unused medication. Participants will be asked to complete the PHQ-9, QSU, MED-Q, and TLFB in-person. Suicidal risk will be assessed using the MINI Suicidality section (B).

6.9 Visit H: Week 24 Post-TQD Follow-up Visit (Approximately 20 minutes in-person)

At the in-person visit, we will measure breath CO level and participants will be asked to complete the PHQ-9 and TLFB. Visit may be completed at same time as inpatient hospital visit or the outpatient postpartum visit.

6.10 Visits I & J: Postpartum Week 2 and Postpartum Week 6 Visits (Approximately 25 minutes by telephone or in person)

At each visit, participants will be asked to complete the PHQ-9 and TLFB by telephone. They will then receive a 10-minute booster counseling session. The session will focus on reinforcing success and reviewing the quit plan (for participants who have quit smoking) or re-establishing a quit date and restarting the cessation process (for participants who have relapsed to smoking). Women who have failed to stop smoking or have relapsed will be referred for counseling by staff at the obstetrics clinic from which they were recruited and at which they will be receiving early postnatal care.

6.11 Early Termination Visit (Approximately 30 minutes, in-person or divided between in-person and telephone sessions)

Participants who discontinue treatment prematurely will be asked to complete an end-of-treatment evaluation and all scheduled assessments to facilitate intention-to-treat (ITT) analyses. Participants will be informed of these procedures prior to study enrollment. Participants who terminate participation in the treatment prior to Week 10 will also be asked to complete the scheduled end-of-treatment (Week 10) procedures. For this and any other visit that cannot be completed in-person, assessments will be conducted by telephone.

6.12 Other Study Procedures and Considerations

Screening and baseline visits cannot occur on the same day. The maximum time permitted to elapse between completion of the screening visit and completion of the baseline visit is 30 days. Every effort will be made to complete visits within a 3-day window before or after the date scheduled for the visit as shown in Table 2. However, because the analysis will by intent-to-treat, we will reasonably accommodate subjects' time constraints by extending the window as needed to complete all study visits. During the week prior to each of the visits (B through J), a reminder call will be made to the participant concerning the next scheduled visit. At the reminder call for Visit H (24 weeks post-TQD) the participant will be asked whether she had smoked at all during the previous week. Visit H will be held plus or minus 28 days from the scheduled 24 week post-TQD. This large window accommodates changes in delivery dates and also allows the visit to coincide with the inpatient delivery or the 6-week post-partum office visit, an important convenience for a new mother. If she acknowledges having smoked, an in-person visit is not required but may be held. If she reports no smoking, an in-person visit will be conducted to verify self-report using breath CO measurement. Because breath CO is a non-invasive and simple test, as well as an important outcome measure, we will collect a breath CO reading at all in-person opportunities when feasible, including at time of delivery and at the time of the 6-week post-partum visit. If the blood draw is unsuccessful at the baseline visit, a second attempt will be made at the Week 5 visit. If the second draw is successful, the baseline tubes will also be drawn (for all baseline tests if the participant is still smoking or for DNA only if the participant is no longer smoking). If the second draw is not successful, we will collect DNA from the patient's saliva using the Oragene Discover Kit (PD-LB-00191).

Monthly protocol adherence meetings will be conducted with the coordinators at each site to ensure adherence to the counseling protocol. All sessions, with permission from the participant, will be audiotaped and 15% will be randomly selected for evaluation by Dr. Schnoll using fidelity forms to determine adherence to the elements of the counseling, record the duration of the session, assess the therapeutic relationship and the coordinators' attention to the participants' condition, and provide individual feedback and re-training to the coordinators, as needed. One session from each participant will be selected from among the initial, quit day, or booster sessions for review. The standardized checklists will yield a protocol adherence score (from 1 = "not at all" to 7 = "extensively") and inter-rater reliability will be computed following the model of Shrout and Fleiss (156). This process is modeled on previous cessation clinical trials in pregnant smokers (157) and the general population of smokers (158), which yielded intraclass correlation coefficients of 0.87-0.99. Audio recording is not a requirement of the study and participants will be given the opportunity to opt out. Following evaluation, the recordings will be deleted electronically.

Throughout the study, if a participant misses a study visit due to a vacation or an unforeseen event, study personnel will reschedule the study visit for as soon thereafter as possible. Study staff will mail the study medication to the participant via secure mail or courier under the

supervision of a study nurse or doctor. Participants will only be provided with enough study medication to allow them to maintain their daily dosage of study medication until their next scheduled visit. An investigator will determine how many additional weeks of study medication a participant will be allowed to receive without attending a study visit. In extenuating circumstances, a home visit may be necessary. In those cases, study staff will utilize public transportation (SEPTA), a rental car, or taxi for transportation to and from the visit at the subject's home.

The nurse or coordinator (trained and supervised by the nurse or physician) will provide instructions over the phone on how to take the study medication as per the dosing schedule and record any adverse events that have occurred since the last study visit. Study nurses or coordinators will instruct participants to call our study staff at any time to discuss any problems or concerns they may have while taking the study medication. All participants will be provided phone numbers to contact the study staff during office hours and the pager number for off-hours contact 24 hours a day. Participants will be asked to come in for their next study visit as soon as possible.

7. Statistical Plan

7.1. Power

A power analysis is provided only for the primary aims because the exploratory aim is hypothesis generating. Most of our power calculations were approximated as 2-sided t- or z-tests, with α = 0.05, using PASS Software (Power and Sample Size, NCSS Software, Kaysville, UT). Equivalence testing was approximated as two one-sided tests, with α = 0.025 each.

7.1.1. Aim 1:

The primary efficacy analysis (**H1**) is a comparison in week 10 (of treatment) and week 24 post-TQD of CO-confirmed 7-day point prevalence quit rates for the placebo and bupropion groups. For the week-10 comparison, we expect that the quit rates in the placebo and bupropion arms would approximate those reported in bupropion trials in the general population of smokers (i.e., placebo = 21.2%; bupropion = 35.9%, OR = 2.1; ref. 44). A sample of 360 provides 88% power to detect a significant between-group effect. The OR for bupropion treatment is similar at 24 weeks, based on Jorenby et al. (168) and our own data, and results from 10 and 24 weeks are highly correlated (rho>0.7). Thus, we have 80% power to detect a significant difference between treatment arms.

Safety analyses (**H2**) will examine maternal safety across the 10-week treatment and 24-week follow-up periods and fetal and birth outcomes. Key maternal and fetal outcomes to be compared across treatment groups include rates of moderate-to-severe side AEs of bupropion (from the AE checklist). Key birth outcomes will include Apgar scores, birth weight, duration of pregnancy, rate of obstetrical complications, and need for NICU admission. These analyses will involve a test of equivalence because we cannot use standard statistical tests to conclude that a non-significant comparison shows that the drug is safe (i.e., "the absence of evidence is not evidence of its absence"). In our past study with bupropion, 45% of bupropion-treated participants reported no moderate-to-severe AEs, vs. 47% of participants on placebo, a 2% difference. With the present sample size, we will have 82% power to detect similar equivalence between treatment arms on the frequency of moderate-to-severe AEs over the course of the trial, given that AEs are not significantly different between treatment arms, using an equivalence window of 0.30 to 0.60. Likewise, Oncken et al. (47) reported 38% AEs for the placebo group

and 25% in the nicotine group. An equivalence test with placebo and bupropion groups both at 30% and an equivalence window for bupropion of +/-15% provides 81% power.

For **H3,** we have very high power. Oncken et al. (47) found a difference in birth weight between groups of 337 g, which yields an effect size > d=0.5. The power to detect a difference of that magnitude will exceed 99%, and we have 80% power to detect a difference as small as 180 grams. We also have >89% power to detect differences in secondary analyses of the frequency of low birth weight and preterm delivery.

7.1.2. Aim 2:

Analyses here will assess changes in craving and depression symptom scores as mediators of bupropion treatment effects at weeks 10 of treatment and 24 weeks post-TQD. These measures are continuous difference scores. Our sample of 360 is well above the minimum sample of 200 recommended for such analyses (169-170). The mediation hypotheses will examine the proportion of variance in treatment effect explained (171-172), and we will test each mediation hypothesis with a z-score generated using the delta method. Our sample of 360 gives us 80% power to observe small effects in a 1-sample test (δ = 0.16) when testing at α = 0.05. There are 2 proposed mediating pathways (depression and craving) between treatment and outcome, so our type-1 error will be corrected to 0.025. A sample of 360 gives us 80% power to detect small-to-medium effects (δ=0.35 SD) for changes in the proposed mediators, which we have seen in previous trials (15, 52).

7.2. Statistical Analyses

Dr. Kevin Lynch will oversee analyses, which will be conducted using Stata, SAS, or R-Language software. Preliminary analyses will assess sample characteristics (e.g., dependence, race) by treatment using t-test or contingency table methods. These variables will also be examined for their relationship to completion of outcome assessments. Variables related to treatment arm or completion of follow ups will be included as covariates in analyses of study aims. Compliance measures will be evaluated across treatment arms, and controlled for in primary analyses. We will examine the correlation between self-report and pill count data and week-5 bupropion plasma levels. We will use intent-to-treat as the primary method to evaluate study aims.

7.2.1. Missing Data:

We will examine whether the rate of missing data, primarily our smoking cessation outcome data, is related to a range of potential variables, including treatment arm allocation, and demographic and smoking-related variables. Standard bivariate statistical methods will be used to identify correlates of missing data. Variables associated with the rate of missing data ($p < 0.05$) will be included as covariates in the analyses of aims. Items missing at random from assessments will be imputed prior to calculating final scores using conditional means, estimated with an iterated version of Buck's method (173). We will aim to avoid dropout and missed sessions by keeping participants connected to the trial and motivated to complete measures. In our clinical trials, close monitoring of participants and the use of incentives to offset travel costs have resulted in adherence and retention rates >80% (52). Primary analyses will assume that all participants for whom smoking outcome data are unavailable are smokers (intent-to-treat), which is conventional in smoking cessation research. Because this assumption can attenuate the differences between study groups in quit rates, we will also conduct a "completers-only" analysis, as done previously (174).

7.2.2. Specific Aim 1: To compare the efficacy of bupropion with placebo for smoking cessation in pregnant smokers.

For **H1**, we will test for treatment group differences in a binary abstinence outcome that is a repeated measure using a generalized estimating equations (GEE) model with a logit link. Quit rates at the end of week 10 of treatment and 24 weeks post-TQD will represent our primary outcome variables. Medication group (bupropion vs. placebo) and time point (end of week 10 of treatment and 24 weeks post-TQD) will be treated as categorical predictor variables, and the model will predict separate effects of treatment on abstinence at each time point (an interaction). Our initial analyses will be stratified by site, and we will carefully examine the models for differences by site, testing for an overall interaction. We will use baseline depression (PHQ-9 score of 10) to stratify the randomization. The model may include a small number of covariates added to control error or adjust for confounding [e.g., age, history of pre-term delivery, baseline gestational age, daily smoking rate]. Any variables found to be associated with both outcome and treatment assignment will be entered as covariates. In the absence of an overall interaction (by site), we will pool the study population and account for site in the model as a binary predictor. To evaluate the effectiveness of randomization, we will compare summary statistics for participant characteristics in the two study arms. If there is an imbalance in participant characteristics, statistical adjustment will be used to ensure that the initial results were not biased by it.

Because many participants will fail to become completely abstinent, but may show a reduction in smoking, we will examine cigarette consumption as a secondary outcome. The analysis will be similar to the primary analysis, except that we examine the effect of treatment arm on daily cigarette counts using a GEE model with a negative-binomial link. Likewise, time to (recurrent) event models will be fitted using Cox regression, stratified by event sequence, as in Schnoll et al. (52), to assess lapse and recovery events over 24 weeks.

H2: We will compare treatment arms for equivalence of the frequency of moderate-to-severe AEs (individual and total). The hypothesis test for equivalence is a test of whether the OR is out of the prescribed range for the difference between the treatment arms. Using logistic regression, we will conduct two one-sided tests against predefined upper and lower equivalence boundaries on percent reporting only mild AEs. The test-statistic will be the z-score corresponding to the log of the OR. This provides a more valid test of the potential safety of bupropion for pregnant smokers than a simple comparison of mean responses on a measure of AEs.

H3: Mean birth weight will be compared for treatment groups using a two-sample t-test, in the context of multiple linear regression. The regression format allows us to add covariates to adjust for imbalances in participant characteristics between treatment arms. Treatment will be entered as a binary indicator. In a secondary analysis, we will also compare the percentage of participants in each group that delivers an infant of LBW (1500-2500 g) or preterm delivery. These secondary hypotheses will be tested using the z-score corresponding to the OR that will be estimated using logistic regression.

7.2.3. Specific Aim 2: Assess changes in depression symptoms and craving as mediators of bupropion's effect on quit rates.

We will use a regression-based path model approach to examine mediation of treatment effects based on MacKinnon et al. (175). All variables will be standardized for the analyses. The two suspected mediators will be entered as standardized pre-post differences, continuously distributed and treated as normal in linear regression. The effects of treatment arm on

mediators, and of mediators on outcome, will be assessed using linear regression and standardized variables. We will focus on changes in mediators from baseline to week 3, since abstinence-induced withdrawal effects typically peak within the first 3 weeks of cessation (174), but we can examine delayed changes to weeks 5, 7, and 10 as well. Assuming that treatment predicts our mediators, we will then assemble the path model using standard structural equation modeling approaches. The path model partitions the effect of treatment on outcome into direct (and unexplained) effects vs. mediated effects. We will then test the overall mediation hypothesis using the proportion of treatment effect explained (171-172), and the strength of each mediating pathway. To do this, we will estimate the model for standardized treatment predicting abstinence without mediators to estimate the direct effect of treatment in the unadjusted model ($\hat{\beta}^{\dagger}$). We will then test whether treatment predicts each of the suspected mediators and, in turn, test whether mediators predict abstinence in an adjusted treatment model and estimate the effect of treatment in the mediator adjusted model $\hat{\beta}^{*}$. Finally, we will calculate the proportion of treatment effect explained, which is calculated as $\left(\hat{\beta}^{\dagger} / \hat{\beta}^{*}\right)$; the standard error for this quantity is calculated using the delta method, and the mediation hypothesis will be tested using a z-test. Individual pathways will be tested using products of the coefficients along each path using a delta-method based z-test.

7.2.4. Specific Aim 3: To explore genetic, metabolic, and social/behavioral moderators of the efficacy of bupropion on cigarette abstinence and safety.

These variables may either be continuous, or categorical, and we will address the aim by testing for moderation using the analytical models in Aim 1, testing for interactions with treatment. We will explore whether the risk of AEs and the efficacy of bupropion treatment (vs. placebo) is moderated by: 1) the rate of nicotine metabolism (i.e., NMR) and variation in *CYP2A6*; 2) the rate of bupropion metabolism (i.e., variation in *CYP2B6* and plasma concentrations of bupropion and hydroxybupropion); and 3) variation in social/behavioral variables, including weight concerns, body image, adverse childhood experiences, and the presence of other smokers in the home. Because this is exploratory, we will test at $\alpha = 0.05$, using the z-score for the interaction term for binary or continuous predictors, or the Wald χ^2 for categorical predictors.

7.3. Participant Population for Analysis

Data from protocol-compliant participants will be used for analysis.

8. Safety and Adverse Events

8.1. Definitions

Adverse Event - Maternal

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event - Maternal
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant wellbeing, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event – Neonate

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during gestation or at birth. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance
- results in prolonged hospitalization in the NICU due to neonatal abstinence syndrome (expected for babies exposed to methadone or buprenorphine) or premature birth (expected for babies whose mothers' smoke)
- conditions associated with premature birth, such as patent ductus arteriosus

Serious Adverse Event – Neonate
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE develops or worsens in severity during gestation or at birth that is:

- fatal
- life-threatening
- requires or prolongs hospital stay in the NICU (except for neonatal abstinence syndrome)
- results in persistent or significant disability or incapacity
- results in a congenital anomaly or birth defect
- results in any unexpected condition not explained by gestational history

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the participant wellbeing, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Adverse Event Reporting Period
The study period during which adverse events must be reported will be defined as the period from the initiation of any study procedures to the end of the last assessment.

Pre-existing Condition
A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

At screening, any clinically significant abnormality or disorder should be recorded as a pre-existing condition. At the end of the study, any new clinically significant findings/abnormalities or disorder that meets the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the IRB of any adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The IRB will also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator. Thus, hospitalization for normal childbirth is not considered an adverse event.

8.2. Recording of Adverse Events

At each contact with the participant, an investigator or staff member must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs,

symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3. Reporting of Serious Adverse Events and Unanticipated Problems

8.3.1. IRB Notification by Investigator

A Serious Adverse Event (SAE) must be reported to the IRB within 72 hours of the event. The investigator will keep a copy of this SAE form in the study binder.

At the time of the initial report, the following information will be provided:

- Study identifier
- Study Center
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study participation was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study participation

Significant new information on ongoing serious adverse events should be provided promptly to the IRB.

8.4 Unblinding Procedures

In the event that participants are prematurely discontinued, it will be necessary to avoid breaking the blind whenever possible, in order to protect the integrity of the study. If an emergency necessitates that the blind be broken, only the pharmacist will have access to the unblinding codes and will be given the names of the staff with authority to request that the blind be broken. If the IDS or hospital pharmacy is contacted by other persons in requesting the study blind be broken for a participant, and the study physician is not reachable, the pharmacist will act according to his/her best judgment in deciding whether or not to break the study blind for that participant. The hospital pharmacist can be reached 24 hours a day by beeper to rapidly access participant unblinding codes.

The pharmacy emergency beeper number is: 215-555-1212.

8.5 Medical Monitoring

It is the responsibility of the principal investigator at each site to oversee the safety of the study at that site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will involve regular staff meetings to assess the number and type of adverse events; these meetings will be held separately at the different sites. There will be a single Data and Safety Monitoring Board for the study, which will

meet twice annually to oversee safety issues for the whole study (see Section 10 Auditing, Monitoring and Inspecting).

8.6 Protection of Participants

Complementing the safety measures noted above, additional procedures will be followed to protect the safety of the research participants. Potential participants will be screened for medical illnesses that would preclude the use of bupropion. Participants selected for the study will be evaluated regularly while receiving study drug treatments, both by study staff at periodic visits (as described in Table 2) and by obstetrics staff for their routine prenatal monitoring. AEs will be monitored regularly in-person or by telephone (see Table 2) and a study physician will be available at all times to evaluate and treat adverse effects of the medication. The participants' weight and blood pressure will be monitored during their standard prenatal visits and pulse rate will be measured at all in-person visits (see Table 2). AEs that reflect significant risk to the participant or fetus will result in discontinuation of the study medication, a decision that will be made by the site principal investigator together with the study obstetrician at that site. Venipuncture will be carried out with good aseptic technique by an experienced phlebotomist, nurse, or physician. Venipuncture sites will be monitored carefully for signs of infection. Participants will be given a 24-hour emergency number that they can call if necessary. The physician or nurse will clinically follow all participants who are discontinued due to a serious AE until the AE resolves and becomes completely stable, unless a referral to another physician (i.e., a specialist) is clinically indicated or requested by the participant.

9. Data Handling and Record Keeping

9.1. Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the participant's revocation of authorization. For participants that have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

Records, filed in the IRB office, verify that all research project personnel have completed training in the protection of human research participants in accordance with the guidelines of the U.S. Department of Health and Human Services (DHHS) and the Office for Human Research Protection (OHRP). The study staff (PI, Clinical research coordinator, etc.) will keep all study medical records (including any codes to de-identified data) under lock and key in a secure location, as required by law. Only the date and time of the research visit will be placed in the client's existing electronic medical record. All electronic data and files (e.g., database, spreadsheet, etc.) containing identifiable participant information shall be password protected. Any computer hosting such files shall have a BIOS password to prevent access by un-authorized users. If participant data are to be exchanged with others, the data will be coded. If identification is necessary, then the data will be encrypted while en route to the recipient with

strong encryption levels (≥ 128 bits for symmetric encryption (DES) and ≥ 1024 bits for asymmetric encryption (RSA). All information collected via the social media landing page will be stored securely our Data Management Unit (DMU).

All data and blood specimens will be stored without direct identifiable information, but will be identifiable via a linking code. The secured research records are labeled with code numbers only (names and other identifying information are kept separate from research records). Access to hard copy data is only given to staff members working on the study. Only staff members designated to handle or analyze study samples will have access to the samples and their storage. Coded blood samples are stored in clinic-specific refrigerators and freezers, which are located in secure rooms. As per routine in the CSA, all electronic files (e.g., database, spreadsheet) will be password protected. Any computer hosting such files will have a BIOS password to prevent access by un-authorized users.

Text messaging will be done in conjunction with Sense Health, a contractor with substantial experience in the use of text messaging in health applications. The Sense Health web service was built on top of the Amazon Web Services (AWS) cloud infrastructure, a highly secure and scalable service, that was designed in alignment with HIPAA regulations, standards, and best practices. The underlying code for the web service is version-controlled and securely backed-up on the GitHub.com. A variety of security measures have been implemented to protect PHI:

Administrative Safeguards: All Sense Health staff members are trained to understand the core requirements of HIPAA, and only authorized staff members have access to data stores that contain any PHI. Furthermore, any database containing PHI data is de-identified, so that patient information is protected even if that database is compromised.

Physical Safeguards: All of the Sense Health data and code are stored on secure cloud infrastructures such as AWS and GitHub, which were designed to comply with HIPAA regulations and best-practices.

Technical Safeguards:
Access control: Only authorized staff members can access the Sense Health servers on AWS and the code repository on GitHub. This access is only possible via SSH tunneling. Therefore, only authorized staff members on authorized machines can access the servers and code.

Transmission security: All communication between servers and the outside world is encrypted during transmission using Class 3 SSL certificates on port 443 only.

Data encryption: All PHI data are encrypted and stored on a MySQL AWS RDS database that is inaccessible to the outside world. This information is encrypted *before* it is stored on the database, using standard AES encryption protocols. Therefore, all patient data are de-identified before they are stored at rest.

Data Backups: The Sense Health databases, code, and server images are backed up both daily and hourly and stored on separate AWS availability zones, so that data are never lost and can be easily recovered when needed.

Data Disposal: All PHI can be permanently disposed of when no longer needed by removing those data from all active and backed-up AWS RDS databases.

Blood will be collected for DNA analysis. The information derived from analysis of the participants' DNA will not be provided to the participants, since at the present time the existing preliminary genetic data for predicting response to bupropion do not provide a basis for genetic counseling. Should that situation change over the course of the study, procedures will be developed in conjunction with the UPenn and City of Philadelphia IRBs, to provide participants with relevant information on genotype and to counsel them in relation to that information. While the study is open, DNA samples will be coded with a number that provides an indirect link to the participant's identity (samples will be accessible only by the researchers and staff involved with this study). Upon completion of the study, the sample will be kept in storage indefinitely. However, the sample will forever be separated from all identifiers. These de-identified samples may be shared with other researchers and used in other projects. The lab procedures for storage include a passcode-protected locked room, and secure storage freezers. All samples will be retained securely as per lab protocols.

Data used to process subject payments with the Greenphire ClinCard program is entered electronically using secure web-based interfaces. Greenphire clinicard is HIPAA compliant. Please see document titled, "ClinCard Data Security and Privacy Statement," located in the appendix. The Greenphire system requires completing a W9 for each subject, and entering subject's name, address and social security number.

9.2. Source Documents

Source data consists of all information, original records, observations, or other activities during participation in the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the laboratories.

9.3. Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in blue or black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated.

9.4. Records Retention

It is the investigator's responsibility to retain study essential documents for at least 3 years after the closure of the study with the IRB.

9.5. Blood samples storage and retention.

Blood for both the UPenn and Jefferson sites will be stored in a coded manner in a designated -80 degree freezer at UPenn and shipped to the laboratory of Dr. Rachel Tyndale at the University of Toronto, on dry ice approximately every four months or as necessary for the duration of the study. Samples will be shipped following the University of Pennsylvania's

guidelines for shipping international biological samples. Samples will be coded and protected health information will not be included. DNA extraction and genotyping will be carried out in Dr. Rachel Tyndale's laboratory. The nicotine metabolite ratio (NMR), a genetically informed biomarker based on the measurement of two long-lasting nicotine metabolites (cotinine and 3-hydroxycotinine), will also be measured. Finally, bupropion and hydroxybupropion plasma concentrations will be measured using blood obtained at the week-5 visit.

10. Study Monitoring, Auditing, and Inspecting

10.1. Study Data and Safety Monitoring Plan

This study will be monitored according to the attached Data and Safety Monitoring Plan (DSMP) version 1, dated 7/6/2016 (see Appendix). The DSMP includes 100% source data verification to be performed for each subject, at each site, to ensure that all of the essential aspects of the Sponsor's oversight of the research at all sites are addressed. The Principal Investigator will identify an appropriately trained staff member and allocate adequate time and supervision for such monitoring activities to occur. The Investigator will also ensure that the monitor is given access to all of the study-related documents and, has adequate space to conduct the monitoring visit.

SAFETY MONITORING AND REPORTING PROTOCOL

Adverse Event Determination and Reporting Procedures. For this study, we will use established Penn procedures and infrastructure for data and safety monitoring and a protocol-specific Data and Safety Monitoring Board (DSMB). The specific elements of our plan is as follows: 1) all project staff will complete certification in the protection of research participants; 2) the protocol will be submitted for review to the IRB and all procedures and policies outlined by the IRB will be followed for this study; and 3) a DSMB will be established to review the progress of accrual and the safety of participants. We will supply the designated IRB with ongoing progress reports for the study and a formal review of the study will be conducted annually or more frequently as designated by the IRB. The Penn IRB will act as the IRB of record for both sites per the IRB Authorization Agreement signed by both sites. The City of Philadelphia IRB will receive an annual report and be informed of all SAEs and reportable events. The IRB may suspend, terminate or restrict the study as appropriate. Each participating investigator must complete certification in the protection of research participants. Finally, Dr. Kranzler (at Penn) and Dr. Hand (MATER/Jefferson) will manage the flow of documents to external agencies to facilitate ongoing and timely review. The IRB will audit the study as needed and will review all data on a regular basis at least every 12 months. All serious adverse events (SAEs) will be reviewed on a real-time basis first by the study physicians. An existing protocol for adverse event monitoring and adverse event reporting will be used (see below). The DSMB will consist of four individuals who are not involved in the study: a statistician (Richard Feinn, Ph.D., Assistant Professor of Medical Science at Quinnipiac University), an obstetrician (Samuel Parry, M.D., Associate Professor of Obstetrics and Gynecology at Penn), a clinical trialist (David Oslin, M.D., Professor of Psychiatry at Penn) and a women's behavioral wellness specialist (Neill Epperson, MD, Professor of Psychiatry and Ob/Gyn at Penn). The DSMB will establish guidelines for adverse event reporting. The DSMB will meet annually, with additional meetings, as may be required. Prior to meetings, all members of the DSMB will receive a report describing study progress, including enrollment, treatment completion or early termination, and a summary of all adverse events. A formal data and safety monitoring plan, detailing the DSMB's activities, will be submitted to the IRB for review and approval prior to study initiation and periodic reports will be included with annual IRB reviews.

PARTICIPANT SAFETY MONITORING PROTOCOL

Monitoring Participant Safety. For this trial, we will use a method to track, manage, and report adverse events that was used in completed studies (14, 43, 52) and is being used in an ongoing (U01 DA020830) pharmacotherapy trial. First, in terms of personnel, each clinical site will include a study physician, a study psychologist, and a research nurse/qualified medical staff person to handle comprehensive eligibility screening, monitoring of participant reactions and adverse events, and the management of any adverse events. The initial eligibility screening procedures will involve careful assessment of participants' medical history to ensure that individuals with pre-existing conditions that can increase adverse event risk are excluded. Second, we will use a two-tiered system to assess potential adverse events. Site staff will complete a baseline adverse event checklist (week 0). At weeks 1, 3, 5, 7, and 10, staff members will conduct an open-ended evaluation of any potential adverse event and complete the established checklist of adverse events. Lastly, as done in our previous clinical trials, participants will be provided with contact information (a wallet-size card) so that, if a serious adverse event occurs, they have methods to contact study staff at their respective clinical site 24 hours a day. Because participants may try to communicate regarding adverse events through the daily text messaging service, which will not be monitored for this purpose, we will provide contact information via an auto-message informing the participant of how to reach study staff in an emergency.

For all adverse events, the site nurse practitioner, in consultation with the site PI and the obstetrician at each site (as needed), will determine a course of action (i.e., continuation and monitoring, dose reduction, participant withdrawal). All adverse events that are considered Serious Adverse Events (see below) will be reported to site PIs and IRBs at all clinical sites, as well as to the FDA and NIH (see below for protocol for adverse event reporting). Site PIs and study physicians will determine whether a serious adverse event requires additional care. Such events may be referred to the outpatient department at the clinical site or to the emergency department of the clinical site (all sites have access to 24-hour emergency services, including extensive inpatient and outpatient services for psychiatric conditions).

MEASURES FOR PARTICIPANT SAFETY.

Medication Adverse Events Checklist. An adverse events checklist will assess the frequency and severity of common adverse events associated with bupropion (rated as: none, mild, moderate, or severe). This measure will be conducted at weeks 1, 3, 5, 7, and 10. This assessment is meant to monitor participant safety and reduce or stop treatment if need be. But, adverse events will be considered an outcome and a covariate in the analysis, as the overall frequency and/or as the presence (ever) of specific common adverse events. Our adverse events measure includes items that have been reported from bupropion use. In addition, we will monitor the prenatal care record to identify adverse obstetrical events, which will be recorded and reviewed regularly by the study team at each site. The data will be fully abstracted at the time of delivery for use in data analysis, which will provide a second opportunity to review obstetrical adverse events that may have occurred during the pregnancy.

Open-ended Questions. In addition, open-ended questions concerning adverse events are assessed at these weeks. Staff will probe for physical and psychiatric adverse events. This method is included to supplement standard adverse event measures so non expected adverse events will be captured. Events will be classified as none, mild, moderate, or severe.

PARTICIPANT ADVERSE EVENT REPORTING PROCEDURES.

For any reported adverse event: While with the participant, study personnel will listen, identify, and document the adverse event, which may not be related to medication and may not be a Serious Adverse Event. The protocol for recording adverse events and reporting the event is listed below:

- The symptom MUST be coded by its severity and responded to according to the following protocol (please see tables below for symptom coding).
- Severity Definitions: None = no concerns, Mild = Adverse event does not interfere with usual daily activities; Moderate = Adverse event interferes with some activities; Severe = No normal activities are possible.

	Code 1 Response	**Code 2 Response**	**Code 3 Response**	**Code 4 Response**
Adverse Event Checklist: If adverse event severity is not listed, no report is required unless the participant requests that the study physician be consulted.				
1. Irritability		Moderate	Severe	
2. Irregular heartbeat		Mild Moderate	Severe	
3. Depressed mood	Mild	Moderate	Severe	
4. Increased heart rate or palpitations		Mild Moderate	Severe	
5. Suicidal thoughts, ideation			Any Reporting	
5b. Suicide Attempt				Any Reporting
6. Nausea (without vomiting)		Moderate	Severe	
7. Sleep problems		Moderate	Severe	
8. Constipation		Moderate	Severe	
9. Vomiting		Mild Moderate Severe		
10. Dry Mouth		Moderate	Severe	
11. Gas		Moderate	Severe	
12. Anxiety		Moderate	Severe	
13. Skin swelling or rash		Moderate	Severe	
14. Indigestion		Moderate	Severe	
15. Agitation		Mild	Moderate Severe	
16. Insomnia		Moderate	Severe	
17. Headache		Moderate	Severe	
18. Abnormal dreams		Moderate	Severe	
19. Disturbance in Attention		Moderate	Severe	
20. Diarrhea		Severe		
21. Abdominal Pain	Mild	Moderate	Severe	
22. Flatulence		Moderate	Severe	
23. Dizziness		Moderate	Severe	
24. Fatigue		Moderate	Severe	
25. Feeling of Weakness		Moderate	Severe	
26. Skin Redness		Moderate	Severe	
27. Hostility		Mild	Moderate Severe	
28. Chest pain		Mild Moderate	Severe	

29. Weakness of one or both sides of the body		Mild Moderate	Severe	
30. Blurred vision		Mild Moderate	Severe	
31. Sweating			Severe	
32. Strange taste			Severe	
33. Ringing in ears		Mild Moderate	Severe	
34. Tremors		Mild Moderate	Severe	
35. Seizure				Any Reporting
36. Fainting (loss of consciousness)			Any Reporting	
37. Confusion		Moderate	Severe	
38. Muscle aches		Moderate	Severe	
39. Shortness of Breath		Mild	Moderate Severe	
Open-ended Responses *(this is not an exhaustive list)*				
1. Allergic reaction	Mild	Moderate	Severe	
2. Appetite loss	Moderate	Severe		
3. Asthma		Moderate	Severe	
4. Blood pressure increase		Moderate	Severe	
5. Cancer				Any Reporting
6. Change in taste perception		Moderate	Severe	
7. Chest pain		Mild	Moderate Severe	
8. Trouble concentrating		Moderate	Severe	
9. Death				Any Reporting
10. Emergency Room Visit				Any Reporting
11. Heart Attack/MI				Any Reporting
12. Heartburn		Moderate	Severe	
13. Hospitalization				Any Reporting
14. Itching		Moderate	Severe	
15. Lightheadedness	Mild	Moderate Severe		
16. Nose Bleed		Moderate Severe		
17. Neurological event Stroke/TIA, etc				Any Reporting
18. Psychiatric event (not related to suicide)		Mild	Moderate Severe	
19. Racing thoughts		Moderate	Severe	
20. Runny nose		Moderate	Severe	
21. Sore throat		Moderate	Severe	

Code 1 Events

- Documented either on Adverse Event Checklist or on Open-Ended AE Form

- If reported at a scheduled visit, email sent to Site PI, Site Study Physician, and Site Coordinator for review within **72 hours**

  Email should be based on the following template:

Today, an adverse event assessment with participant XXXXXXX was completed. This session was conducted at week X, X weeks after study medication was initiated. During the assessment the participant reported [mild/moderate/severe] _____ (Code X).

This adverse event was (or was not) reported at a previous assessment.
The participant is currently/not currently smoking and is/is not on protocol with taking study medication.

- Internally reviewed by the PI and/or Study Physician.
- Response printed out and filed in the participant chart.
- The participant will continue in the trial unless they decline to do so. Medication can be continued.

- The physician can evaluate the information presented in the email along with any further information received from contact with the participant and, based on clinical judgment, change the code that the event received (either increasing in severity or decreasing in severity).

- If reported to site staff ***between scheduled sessions,*** email sent to PI, Study Physician, and Study Coordinator for review within 48 hours as above.

Code 2 Events

- Documented either on Adverse Event Checklist or on Open-Ended SE Form

- If reported at a scheduled visit, email sent to Site PI, Site Study Physician, and Site Coordinator for review within **24 hours** (obstetrician to be consulted, as needed).

  Email should be based on the following template:

  Today, an adverse events assessment with participant XXXXXXX was completed. This session was conducted at week X, X weeks after study medication was initiated. During the assessment the participant reported [mild/moderate/severe] _____ (Code X).

  This adverse event was (or was not) reported at a previous assessment.

  The participant is currently/not currently smoking and is/is not on protocol with taking study medication. Please let me know whether - after your review - the SEC codes should be modified &/or if further action should be taken.

  - Internally reviewed by the site PI and/or Study Physician.
  - Response printed out and filed in the participant's research chart.
  - Participant may continue medication unless she thinks that the medication is making her symptoms worse or wants to stop (or the Study Physician tells her to stop).
  - Dose adjustments can also be considered.
  - The Study Physician will follow-up with the participant as deemed appropriate.

- The study physician/PI can evaluate the information presented in the email along with any further information received from contact with the participant and, based on clinical

judgment, change the code that the event received (either increasing in severity or decreasing in severity). The SEC data may be changed accordingly.

If reported to site staff ***between scheduled sessions,*** email sent to PI, Study Physician, and Study Coordinator for review within 24 hours as above

Code 3 Events

- Regardless of when Code 3 events are reported, they will be considered urgent and follow-up will be immediate.

- Staff can advise participants to contact their physician immediately or call 911.

- If the participant is currently taking study medication, she will be instructed to discontinue the medication pending additional consultation with her doctor or a Study Physician.

- ***If reported during a visit, the site physician and/or PI will be notified immediately by phone or in-person to address the report immediately (see template below for call).*** The physician may be contacted via pager so that the situation can be resolved quickly. The study doctor will evaluate the problem and, if needed, contact the maternal-fetal medicine attending (during regular hours) or the maternal-fetal medicine fellow on-call (during off hours).

- An email is also sent for documentation as follows to the study physician, PI and coordinator.

  Email (or conversation) should be based on the following template:

  Today, an adverse events assessment with participant XXXXXXX was completed. This session was conducted at week X, X weeks after study medication was initiated. During the assessment the participant reported [mild/moderate/severe] _____ (Code X).

  This adverse event was (or was not) reported at a previous assessment.

  The participant is currently/not currently smoking and is/is not on protocol with taking study medication. Please let me know if - after your review - the SEC codes should be modified &/or if further action should be taken.

  - Study Physician will oversee recommendations and follow-up with the participant until the event is resolved or the participant is stable.
  - Study Physician will report to the PI.
  - Response printed out (or conversation documented) and filed in the participant's research chart.

- The physician can evaluate the information presented in the email/telephone call or in-person assessment along with any further information received from contact with the participant and, based on clinical judgment, change the code that the event received (either increasing in severity or decreasing in severity). The SEC data may be changed accordingly.

- These events may be considered Serious Adverse Events, requiring additional reporting

(see below).

- If reported to site staff ***between scheduled sessions,*** email or phone call to PI, Study Physician, and Study Coordinator for review immediately, following the procedures above.

Code 4 Events

- Code 4 events may not be associated with bupropion use, but will be recorded and immediately reported to the entire Research Team.

- Code 4 events are considered urgent and follow up will be immediate.

- Code 4 events are serious, unanticipated health events that happened after enrollment/since the last call (i.e. requiring MD, ER or hospital care). These include death, MI, stroke, transient ischemic attack, cancer diagnosis, pneumonia or COPD/Asthma/CHF exacerbation. Hospital visits for non-life threatening events or anticipated procedures may not require study withdrawal.

- If applicable, staff can advise participant to contact her physician immediately or call 911.

- If the participant is currently taking study medication, she will be instructed to discontinue the medication pending additional consultation with their doctor or the Study Physician.

- ***If reported during a visit, the site physician and/or PI will be notified immediately by phone or in-person to address the report immediately (see template below for call).*** The physician may be contacted via pager so that the situation can be resolved quickly. The study doctor will evaluate the problem and, if needed, contact the maternal-fetal medicine attending (during regular hours) or the maternal-fetal medicine fellow on-call (during off hours).

  Email (or conversation) should be based on the following template:

  Today, an adverse events assessment with participant XXXXXXX was completed. This session was conducted at week X, X weeks after study medication was initiated. During the assessment the participant reported [mild/moderate/severe] _____ (Code X).

  This adverse event was (or was not) reported at a previous assessment.

  The participant is currently/not currently smoking and is/is not on protocol with taking study medication. Please let me know if - after your review - the SEC codes should be modified &/or if further action should be taken.
  - Study Physician will oversee recommendations and follow-up with the participant until the event is resolved or the participant is stable.
  - Study Physician will report to PI.
  - Response printed out (or conversation documented) and filed in the participant chart.

- The physician can evaluate the information presented in the email/telephone call or in-person assessment along with any further information received from contact with the

participant and, based on clinical judgment, change the code that the event received (either increasing in severity or decreasing in severity). The SEC data may be changed.
- These events may be considered Serious Adverse Events, requiring additional reporting (see below).
- If reported to site staff ***in between scheduled sessions,*** email or phone call to PI, Study Physician, and Study Coordinator for review immediately, following the procedures above.

Additional Reporting Requirements (IRB, NIH, FDA)

Reporting

- The study site coordinators are responsible for reporting adverse events that are considered serious adverse events to their IRB
- Generally only Code 3 or Code 4 events would be classified as Serious Adverse Events, reportable to IRBs, NIH, and FDA
- Note that the a Serious Adverse Event may not be related to the participant's treatment.
- Any death is a Serious Adverse Event, and shall be reported immediately whether it is related to study participation or not.

Reporting of Serious Adverse Events (SAEs)

Serious Adverse Event Definition. An SAE is any adverse event, without regard to causality, that is life-threatening or that results in any of the following outcomes: death; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability or incapacity; or a congenital anomaly or birth defect. Any other medical event that, in the medical judgment of the Principal Investigator, may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. A planned medical or surgical procedure is not, in itself, an SAE.

SAE Reporting Period. The SAEs that are subject to this reporting provision are those that occur from after the first dose of study medication through 28 days after discontinuation of study medication. Study staff will assist FDA or other regulatory staff in investigating any SAE and will provide any follow-up information reasonably requested.

SAE Reporting Procedures. If an event is to be classified as a Serious Adverse Event (SAE), the following reporting procedures must be followed:

- Code 3 event (with hospitalization, disability), reported to site IRB, all Site PIs (using Adverse Event Reporting Form below), NIH and the FDA (using MEDWATCH FORM) within 72 hours.
- If Code 4 event, reported to site IRB, all Site PIs (using Adverse Event Reporting Form below), NIH and the FDA (using MEDWATCH FORM) within 24 hours.
- Reports to the site's IRB may use site-specific forms as needed.
- Reports to other sites must use the Adverse Event Reporting Form below.
- Reports to NIH and FDA must use the MEDWATCH (http://www.fda.gov/medwatch/index.html). The Medwatch form is submitted directly to the FDA and to the IRB.

Contact Information:

Food and Drug Administration: Telephone 1-800-FDA-1088; Fax 1-800-FDA-0178; Internet http://www.fda.gov/medwatch/report.htm

MedWatch: The FDA Safety Information and Adverse Event Reporting Program; Food and Drug Administration; 5600 Fishers Lane; Rockville, MD 20857-9787

Diagram of Protocol (To Guide Reporting)

Step #1: Identify AE or Adverse Drug Event/Reaction (Treatment Adverse event Checklist completed)

2 Adverse Event
An untoward deviation from baseline health occurring from the time the patient signed consent

1 Adverse Drug Event or Reaction
An untoward medical occurrence identified after initiating study treatments where there is a reasonable possibility that the event may have been caused by treatment

Step #2: Determine Severity of Event/Reaction (Treatment Side Effect Checklist will be completed)

Code 1 **Code 2** **Code 3** **Code 4**

Step #3: Determine Cause of Event/Reaction (Consult physician/psychologist, PI and literature)

Unrelated = not related ** Unlikely = doubtfully related ** Possible = may be related
Probable = likely related ** Definite = related

Step #4: Determine if Event/Reaction is Expected (Consult physician, PI and literature)

Step #5: Determine if Event/Reaction is Serious Adverse Event/Reaction (Consult physician/PI and literature)

- Is life-threatening, disabling, or fatal?
- Results in birth defect?
- Requires serious medical/surgical intervention

Step #6: Reporting Adverse Events/Reaction

Code 1 → No formal report required

Code 2 and 3 → No hospitalization, not life-threatening, etc. → No formal report required

Code 2 and 3 → Hospitalization, life-threatening, etc. → MD determines hospitalization is not related to study participation → No formal report required

Code 2 and 3 → Hospitalization, life-threatening, etc. → Site MD determines hospitalization, life-threatening event is related to study → Within 3 calendar days, AE Form to:
- IRB/DSMC,
- Grant Agency & FDA

Code 4 → Within 24 hours, AE Form to:
- IRB/DSMB,
- Grant Agency & FDA

10.2. Auditing and Inspection

The investigator will permit study-related monitoring, audits, and inspections by the IRB and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11. Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

11.1. Consent Procedures

All participants for this study will be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study (See Participant Informed Consent Form). This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a participant, using the EC/IRB-approved consent form, must be obtained before that participant undergoes any study procedure. The form must be signed by the participant or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent. The investigator or designee will obtain informed consent before any study procedures occur, explaining all procedures in detail in an individual session. Participants will be assured that their participation is voluntary and that withdrawal from the study would not jeopardize current or future participation in research studies. All participants will be informed of potential risks and benefits involved in the study.

12. Study Finances

12.1. Funding Source

The National Cancer Institute will provide funding for the conduct of this study.

12.2. Conflict of Interest

Any investigator with a conflict of interest (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan. All University of Pennsylvania investigators will follow the University of Pennsylvania's conflict of interest policy. All Thomas Jefferson University investigators will follow Thomas Jefferson University's conflict of interest policy

12.3. Participant Payments

Participants will be paid for their travel costs, time spent, and returned study medication blister packs. The maximum amount to be paid is $360-$375 for full participation (the $15 difference being based on whether the 24-week visit is in the clinic or either by telephone or at the hospital) and returning all of the study medication blister packs. The amount will be prorated based on the actual complement of study assessments completed and the number of study medication blister packs returned. Payments will be made at each in-person study visit and will include payments for telephone visits completed since the last in-person visit. Participants will

also receive a baby gift of a box of 42 size 2 diapers and a tub of 40 baby wipes at either the Week 10 or the Week 24 visit (approximate value of $15 for both). Participants will also have the option to receive a cell phone with coverage for text and talk, at no cost. Payments will be made via Greenphire ClinCards. Clincards are reloadable prepaid cards that may be used for in-store purchases (by selecting either the “credit” or “debit” option) and online purchases. Cash may be obtained using the ClinCard at a bank for no fee or at an ATM for a fee of up to $2.50.

Table 3: Schedule of Participant Payments

Visit		Time Spent	Travel Costs	Return Medication Pack(s)& Phone	Total for Visit
Visit A: Screening (IP)		$10	$15		**$25**
Visit B: Baseline (IP/T)		$60	$15		**$75**
Visit C: Week 1 (IP)		$35	$15	$1	**$51**
Visit D: Week 3 (T)		$10			**$10**
Visit E: Week 5 (IP)		$35	$15	$4	**$54**
Visit F: Week 7 (T)		$10			**$10**
Visit G: Week 10 (IP)		$30	$15	$5	**$50**
Visit H: Week 24	Phone or In-person	$45 $45	$0 or $15		**$45** **Or** **$60**
Visit I: 2 Weeks postpartum (T)		$10			**$10**
Visit J: 6 Weeks postpartum (T)		$10		Return Phone: $20	**$30**
Total payment for full participation		**$255**	**$75 or $90**	**$30**	**$360 or $375**

IP=In-person, IP/T=In-person, +/- by telephone, T=By telephone, PP=Postpartum
*$1 for each medication blister pack returned

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Appendix

DATA AND SAFETY MONITORING PLAN (DSMP)

TITLE: Placebo-controlled trial of bupropion for smoking cessation in pregnant women

Principal Investigator(s): Henry Kranzler, M.D.

Regulatory Sponsor: University of Pennsylvania

Version #1

Version Date: 7/6/2016

Monitoring

The monitoring of a clinical trial is an essential element of study processes designed to ensure the protection of the subject's rights, the safety of subjects enrolled in the trial and the integrity and quality of the resulting data. This Monitoring Plan (MP) describes the specifications for monitoring. This study monitoring is based on risk. The study shall adhere to the requirements described in the protocol, the International Conference on Harmonization (ICH) and FDA Good Clinical Practice (GCP), and Sponsor SOPs.

Sponsor Monitor

The Sponsor will appoint a qualified Monitor to review and evaluate study data and activities. The Sponsor will provide a monitoring plan and associated documents (protocol, Informed Consent Form (ICF), Standard Operating Procedures (SOPs), and an Investigator's Brochure (IB) to the Monitor. The Monitor will be qualified by education, experience, and training of Good Clinical Practice requirements as well as regulatory compliance. The Sponsor will evaluate any financial conflict and will ensure resources are available to carry out monitoring activities. Training with the protocol, CRFs, ICF, and DSMP will be provided by the Regulatory Sponsor prior to study commencement. The Sponsor is responsible to ensure that appropriate monitoring is occurring as per regulations, 21 CFR 312.50 and 312.56.

DSMB

In addition to the Sponsor Monitor, a DSMB will be utilized based on the risks associated with the study.

The DSMB is a group of individuals who are independent from the study team and are charged with providing expertise and recommendations based on the real time review of trial related data. The DSMB shall review the Monitoring Plan prior to study initiation and accept or provide comments to the Sponsor.

- The DSMB reviews study data for subject safety, study conduct and progress, and efficacy. The DSMB can make recommendations concerning the continuation, modification, and/or termination of the study.
- The Sponsor selects each member of the DSMB. In selecting members to serve on a DSMB, consideration of each person's relevant expertise, experience in clinical trials and in serving on other DSMBs, and absence of serious conflicts of interest is necessary. Members of the DSMB must have no direct involvement in the conduct of the study. Each member's qualification will be documented.

Monitoring Plan

This monitoring plan lists the approach to monitoring the clinical trial and is risk-based. Sponsor oversight focuses on activities to prevent or mitigate important and likely risks to data quality and to processes critical to human subject protection and trial integrity.

Monitoring activities include:

- Oversight of Investigator conduct, including supervision of study site staff and data reporting
- Review of the study site's processes and procedures (e.g., process for investigational product administration)
- Review of site records for completeness and accuracy
- Ongoing evaluation of safety data and the emerging benefit-risk profile of an investigational product
- Review of recruitment rates

- Review of protocol deviations and non-compliance
- Review of subjects who dropped out
- Review of the timeliness of data collection and submissions to the Sponsor
- Verification that informed consent was obtained appropriately
- Verification of adherence to the protocol, including eligibility criteria, study test and procedures, investigational product accountability
- Verification of the disposition of the investigational product
- Review of evaluation, assessment, documentation and reporting of Adverse Events
- 100% source data verification will be performed for all subjects.

Requirements for communicating monitoring results:
The Study Monitor shall share Monitoring visit reports (MVRs) with the Sponsor/Investigator. Safety concerns will also be shared with the Sponsor/Investigator. Within 10 business days of a monitoring visit, the Monitor will prepare the Monitoring Visit Report (MVR) and submit it to the Sponsor.

Managing non-compliance:
Any non-compliance issues arising will be managed in working with the study Investigators.

Ensuring Quality Monitoring:
The Sponsor will meet with the Monitor twice a year, following the monitoring visit, to ensure quality monitoring.

The investigational product, bupropion has a greater than minimal risk safety profile for the mother. Prior experience in human and animals raises safety concerns. The risks associated and potential safety concerns inherent to the study are that bupropion commonly causes dry mouth, insomnia, and dizziness. Other common adverse effects of bupropion runny nose, neck pain, loss of appetite, nausea and vomiting, rash, itching, dry skin, sweating, tremor, abdominal pain, constipation, agitation, muscle or joint pain, urinary frequency, sleepiness, abnormal thinking, bronchitis, hives, strange taste in the mouth, weakness, fever, headache, depression, irritability, and blurred or double vision. Rare, but serious, complications that may be related to bupropion include seizures or hypomania.

For the developing fetus, there is a greater than minimal risk safety profile. Preclinical data indicate that bupropion administered orally to rats and rabbits at doses up to 450 and 150 mg/kg/day, respectively, showed no clear evidence of teratogenic activity. A slightly increased incidence of fetal malformations and skeletal variations were observed in rabbits. Decreased fetal weights were seen at doses of 50 mg/kg and greater. In another study, rats administered bupropion at oral doses of up to 300 mg/kg/day throughout pregnancy and lactation produced offspring showing no apparent adverse developmental effects. One retrospective study examined 7,005 antidepressant-exposed pregnancies in a managed-care database. The study showed no greater risk for congenital malformations among the 1,213 bupropion-exposed first-trimester pregnancies than for other first-trimester antidepressant exposures or to bupropion use during the second or third trimesters.

Enrollment will take place at the University of Pennsylvania and Thomas Jefferson University.

For all subjects consented the Monitor will perform:
- Review of informed consent form (ICF) and informed consent process
- Verification of eligibility (i.e., review of inclusion/exclusion criteria)

- Assessment of treatment compliance
- Review of subject evaluations, testing and follow-up per the protocol
- Assessment and follow-up of safety issues
- Review and comparison of source documents and CRFs for completion and accuracy
- Investigational agent accountability and adherence to product labels
- Review any regulatory documents for amendments/modifications/updates

Timing and Frequency of Monitoring Visits:
On-site monitoring activities will occur based on the high level of risk in the study. Monitoring visits will be done twice each year that the study is active.

The first monitoring visit will be held no later than four weeks (and no earlier than two weeks) after the baseline visit of the first subject in any new site added. Subsequent monitoring visits will take place twice each year.

A study closeout visit at each active site will be conducted no later than 1 month after the final subject has completed the study at that site.

Review of the Informed Consent Form
Review the ICFs to verify that consent was obtained in accordance with regulations and guidelines.

Regulatory Document Review
The site regulatory documents will be maintained in the site regulatory binder. The regulatory binder will be reviewed by the Monitor at each monitoring visit. The Monitor will review the binder to ensure its completeness and that study documents are filed appropriately in a timely manner.

Adverse Event (AE) and Serious Adverse Event (SAE) Reporting
AEs: The Monitor will confirm during review of the collected data and source data/documentation that AEs have been reported as required by the FDA.

SAEs: All will be reported to the Sponsor using MedWatch or CIOMS forms and submitted to the corresponding IRB as per that committee's requirements.

14.2 ClinCard Data Security and Privacy Statement (*dated 14 January 2016*)

Confidentiality of Protected Health Information (PHI)

All clinical trial participant information is stored securely. Greenphire does not sell, use or distribute clinical trial participant information for any purpose other than those needed to execute, service and maintain the ClinCard program (including ClinCard Direct Deposit and Travel Reimbursement methods).

Greenphire protects the privacy of Electronic Protected Health Information ("EPHI"), disclosed or provided to us in compliance with the Security Standards for the Protection of Electronic Protected Health Information at 45 CFR Sections 160 and 164 (the "Security Rules"). Towards that end, Greenphire has implemented administrative, physical, and technical safeguards (detailed below) that reasonably and appropriately protect the confidentiality, integrity, and availability of EPHI; ensures that any agent or subcontractor to whom we provide EPHI agrees to implement reasonable and appropriate safeguards to protect it; and will report any Security Incident involving EPHI of which it becomes aware within five (5) days of learning of the Security Incident.

Data Information Security

As a matter of policy and commitment to clients and clinical trial participants, Greenphire takes great strides to protect all information relating to cardholders. Greenphire has deliberately designed its payments and communication platform including all of Greenphire's externally facing web tools to actively protect all data transfers and data stored with Greenphire's infrastructure:

Database and Encryption– All passwords within our database are protected using the one-way SHA1 algorithm to encrypt passwords, which are then encrypted by the one-way MD5 algorithm. Where necessary, Greenphire's platform makes use of encryption using the 256 bit Advanced Encryption Standard (AES or otherwise known as Rijndael), which is one of the most popular algorithms used in symmetric key cryptography. AES is approved by the US National Intelligence Agency (NSA) for top secret information.

Web Tools – All of Greenphire's web tools that are involved in transferring data between an end-user's web browser and Greenphire's platform (and vice versa) are secured by 256 bit Secured Socket Layer (SSL) with TLS 1.2 encryption. Greenphire is able to track the activities performed on accounts by site administrators through a system of unique logins which allow users access to the clincard.com web tool. In addition, all user activities in the Greenphire Platform are auditable.

Financial Data Transfer - Communications between the Greenphire platform and financial networks are executed via Web Service (API) or sFTP transport.

Physical Protection – Greenphire houses its internal database on servers that are located in a highly secure, off-site facility. Access to the physical servers at the facility is limited to Network Operations Center (NOC) Engineers and Technicians. The facility is secured with a bio-metric security system that can track access to the facility and is monitored by digital security video surveillance, includes multiple suppliers for network connectivity and redundant power supplies including on-site power generation in the event of emergency.

Authorized Access – Greenphire restricts access to sensitive data to only a limited number of essential internal personnel. Authorized individuals are only permitted to access data

if it is required to service our client, their authorized users or the clinical trial participant. The number of authorized individuals remains limited to protect against internal threats to the security of sensitive data.

Proactive Design - Greenphire's internal technology platform has been intentionally designed to exclude the requirement of certain sensitive information that other similar companies require to be stored in their systems, such as PIN numbers. If new types of sensitive data must be introduced and stored, per the design of a specific protocol, Greenphire will protect the data using the encryption methods described previously.

Customer Service - Greenphire provides all of its cardholders with 24/7/365 customer service. Customer service is handled by both an automated IVR system and a call center where live customer service representatives may provide financial assistance to cardholders. Customer service functionality is intentionally kept separate from implementation and client support and, consequently, no information is shared with customer service representatives related to the protocol, sponsor, structure of the trial, medical indication or other potentially sensitive information.

Quality Control Process - Greenphire's Quality Control (QC) Department performs system testing in an isolated environment to test and ensure that the software is functioning properly. Each new piece of functionality is thoroughly tested individually. In addition, QC conducts integration and regression testing before new code is approved for movement into production. When a change to the system necessitates a change to the database, the required changes and process to make the changes are documented and tested prior to being performed on production. No code is pushed to production until it has passed QC testing. Data used in QC is test data and does not include data that is, or ever was, production data.

Safe Harbor

Greenphire has voluntarily obligated itself to the jurisdiction of the U.S. Department of Commerce by self-certifying to the Safe Harbor framework necessary to receive personal data from companies doing business in the European Union and Switzerland.

Further information regarding the U.S. – EU and U.S. - Swiss Safe Harbor Frameworks is available at export.gov/safeharbor/index.asp