

Nicotine Replacement for Smoking Cessation During Pregnancy

Nicotrol[®] Inhaler (nicotine inhalation system)

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Sponsor:	NICHD
IND No:	104,914
Version:	7.8
Date of Version	January 18, 2016
Participating Institutions:	University of Connecticut Health Center Hartford Hospital Baystate Medical Center

Protocol Sign Off

Protocol title: Nicotine Replacement for Smoking Cessation During Pregnancy

Protocol version: 7.8

Protocol issue date: January 18, 2016

I agree to do the following:

- To perform the study in accordance with the procedures set out in the study protocol
- To ensure that all persons assisting with the trial are adequately informed about the protocol and any amendments
- To perform the study in accordance with the current version of the Declaration of Helsinki, ICH-GCP and in accordance with local ethical, legal and regulatory requirements
- To perform Investigator related tasks in conformity with the Institutional Review Board SOP and FDA regulations. In addition to comply with local requirements on data protection and privacy legislation
- Not to enroll the first patient into the study until I have received written approval from appropriate ethics committee, where applicable and local legal requirements have been fulfilled

UHC	Principal Investigator Name:
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Date: _____	Principal Investigator Signature:
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Site : _____	Investigator Name: (Print)
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Date: _____	Investigator Signature:
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PROTOCOL VERSION # AND/OR DATE: Version #7.8 January 18, 2016

1. Title: Nicotine Replacement for Smoking Cessation during Pregnancy

2. Background:

A.1. Importance of the Problem: Cigarette smoking during pregnancy is one of the most important modifiable causes of poor pregnancy outcomes in the United States [8, 9]. Although maternal smoking increases the risk of spontaneous abortion, placental complications, preterm delivery, and fetal and neonatal death, the most consistent effect is low birth weight (LBW, i.e., <2500 grams) [8, 10, 11]. Maternal smoking doubles the risk of delivering a LBW neonate [12]. LBW neonates, particularly those weighing <1500 g, have exponentially greater morbidity and mortality than normal weight infants [13]. In the US, maternal smoking is responsible for 30% of LBW babies, 10% of premature deliveries, and 5% of all infant deaths [14]. Nicotine affects nervous system development in animal studies, and similar effects have been observed in babies born to women who smoke. Smoking cessation during pregnancy has numerous health benefits; by 16 weeks gestation [15, 16], or even as late as the third trimester [16], cessation results in a near-normal birth weight infant. Smoking reduction also has beneficial effects on birth weight [17]. Because smoking has serious health risks for the mother and infant, robust efforts are needed to help pregnant women quit smoking.

Despite the risks, the majority of women who are smoking when they become pregnant continue to smoke throughout pregnancy. Women who quit smoking usually do so before their first prenatal visit and women who smoke into the second trimester are much less likely to quit [18]. These women are more likely to be single, heavier smokers (>1/2 pack per day), and to have a partner who smokes [19, 20]. Less educated women with greater nicotine dependence are particularly likely to continue smoking during pregnancy [19].

Behavioral treatments during pregnancy are consistently but only modestly effective in helping pregnant women quit smoking [2, 21]. A recent meta-analysis of studies of augmented psychosocial interventions of at least 3 minutes duration (e.g., discussing the risks of smoking and benefits of cessation, providing self-help materials) that used biochemical verification of abstinence [2] showed mean cessation rates of 13.3% in the intervention group and 7.6% in the usual care group [2]. Similarly, a meta-analysis of 64 randomized and quasi-randomized trials (with a total of 28,000 subjects) [21] showed a significantly greater reduction of risk in the intervention groups (RR = 0.94; 95% CI = 0.93-0.95), such that 6% more women quit with a behavioral intervention than with usual care.

Despite their potential value for smoking cessation, augmented behavioral interventions are least effective in heavier smokers [22]. The estimated quit rate for behavioral counseling is 20% in women who smoke <10 CPD, while women who smoke 10-19 CPD have a 15% quit rate, and women who smoke >20 CPD have only a 5% chance of quitting [22]. Moreover, the majority of pregnant smokers, even light smokers, do not quit smoking during pregnancy, even with augmented behavioral interventions [21].

In summary, smoking has serious health risks for the mother and infant, and robust efforts are needed to help pregnant women quit smoking. Most women do not quit smoking during pregnancy, this is particularly true for women with less education and heavier smokers. Behavioral interventions have a modest, but consistent, beneficial effect on quitting, but are least effective in heavier smokers.

A.2. Addressing a Critical Barrier to Progress in the Field: Evaluating the utility of medications for pregnant smokers is important because current best practice treatments help only a small minority of

pregnant women to quit smoking. Women who continue to smoke after learning of their pregnancy and of the risks to the fetus may be more dependent smokers who are less able to quit with a behavioral intervention alone [22]. Indeed, one survey shows that pregnant women report nicotine withdrawal symptoms and cravings as major reasons for their inability to quit smoking during pregnancy [23].

Medications are a first-line treatment for smoking cessation in non-pregnant smokers and could enhance smoking cessation rates during pregnancy [2]. Nicotine replacement therapies (NRTs) aim to replace the nicotine usually obtained by smoking, thereby relieving cravings and withdrawal symptoms [24,25]. Compared to placebo, the odds ratio [OR (95% CI)] of abstinence with nicotine gum is 1.5 (1.2-1.7), with the patch it is 1.9 (1.7-2.1), with the inhaler it is 2.1 (1.5-2.9), and with the nasal spray it is 2.3 (1.7-3.0). Bupropion SR, a non-nicotine medication that inhibits the neuronal reuptake of dopamine and norepinephrine [26], has an OR of 2.0 (1.8-2.2). Varenicline, an $\alpha_4\beta_2$ nicotinic receptor partial agonist [27], has an OR of 3.1 (2.5-3.8). All of these medications are effective for this indication and none is preferred for smoking cessation. The utility of any treatment in an individual patient depends on the safety, tolerability, and perceived helpfulness of the agent.

The use of medication could be particularly beneficial in enhancing quit rates during pregnancy. Some nicotine withdrawal symptoms (e.g., irritability, anxiety, difficulty concentrating, insomnia, restlessness, increased appetite, depressed mood, drowsiness) are also commonly experienced during pregnancy [28]. Because these symptoms are present in pregnant smokers before the initiation of cessation, it may be more difficult for these women to quit because of the additional symptoms of withdrawal [23]. Further, the clearance of nicotine is accelerated during pregnancy, so pregnant smokers may need higher doses of replacement therapy than non-pregnant smokers to optimize efficacy [29]. Finally, pregnancy is associated with markedly elevated levels of progesterone, which is postulated to contribute to heightened withdrawal during the late luteal phase of the menstrual cycle [30]. Consequently, medication may be especially efficacious for smoking cessation in pregnant smokers. Studying the risk/benefit profile of different medications is also important since surveys suggest that 10-30% of practitioners prescribe or recommend NRT for pregnant smokers [31, 32]. ***Medications are safe and effective for smoking cessation in non-pregnant smokers. Research is needed to establish their efficacy and safety in pregnant smokers.***

A.2.a Effectiveness studies of medications for smoking cessation during pregnancy: Three randomized controlled trials (RCTs) collectively have shown that NRT may be effective for smoking cessation during pregnancy [33-35]. We did not find any effectiveness studies utilizing bupropion SR or varenicline for smoking cessation during pregnancy. In one NRT effectiveness study, pregnant women who smoked at least 5 CPD received cognitive-behavioral counseling (CBT) and were randomized 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/CBT group had twice the serious adverse event (SAE) rate of the control group. The most frequent SAE in this study was preterm delivery (i.e., delivery at < 37 weeks gestation). However, after adjusting for a history of preterm delivery, the difference in SAE rate between groups was not statistically significant ($p=0.09$). Effectiveness studies suggest that NRT increases quit rates in pregnant smokers. However, without a placebo control, patients' expectations are potential confounders. Thus, although the results of one study have been cited in guidelines and by investigators to call attention to potential safety problems with NRT in pregnancy [2, 36], placebo-controlled studies are needed to examine the safety of this treatment. Further research is also needed to determine whether some individuals are at elevated risk for adverse effects of NRT, which individuals those may be, and the potential mechanisms of these effects. ***RCTs suggest that NRT is effective in enhancing quit rates in pregnant smokers, but one study raised safety concerns. Consequently, randomized, placebo-controlled studies are needed to examine the safety and efficacy of NRT in pregnancy.***

A.2.b Efficacy studies of medications for smoking cessation during pregnancy: Placebo-controlled RCTs are the “gold standard” to assess the safety and efficacy of medications for smoking cessation. Two efficacy studies of NRT with sufficient sample size have been conducted in pregnancy [1, 7]. In a Danish study, all women received counseling by a nurse midwife and either 6 weeks of a nicotine patch (15 mg/16 hours) or a matching placebo [7]. At the end of pregnancy, neither quit rates (28% vs. 25%, respectively) nor the mean number of CPD (7.2 vs. 7, respectively) differed between the groups. However, patch compliance was poor (i.e., the average use being only 2 weeks), which may have reduced quit rates. The authors noted that the Danish Medical Authority advised against NRT use during pregnancy, and this national recommendation may have influenced compliance with treatment in their study. Importantly, however, the mean birth weight was 186 grams (95% CI 35-336) greater in the nicotine group than in the placebo group.

In another placebo-controlled RCT, we recruited 194 pregnant smokers from prenatal clinics to participate in a randomized trial of 2 mg gum or placebo for smoking cessation [1]. Participants received individualized behavioral counseling and were assigned to receive either 2 mg nicotine or placebo gum for 6 weeks followed by a 6-week taper. Biochemically-validated smoking cessation rates were non-significantly higher in the nicotine group at major endpoints (after 6 weeks: 13% vs. 9.6%, $p=0.45$ and at 32-34 weeks gestation: 18% vs. 14.9%, $p=0.56$). Importantly, nicotine produced a greater reduction in CPD and cotinine concentrations than placebo. There was also better treatment retention in the nicotine vs. placebo group. Mean (SD) birth weight and gestational age were also significantly greater in the nicotine group than in the placebo group [3287 g (569) vs. 2950 g (657); $p<0.001$ and 38.9 wk (1.7) vs. 38.0 wk (3.3); $p=0.014$, respectively]. Further, the most striking difference between treatment groups was the greater incidence of babies with LBW and preterm delivery in the placebo group compared with the nicotine gum group (Table 1).

Table 1: Serious Adverse Events in the Nicotine and Placebo Groups

	Placebo (N=87)	Nicotine (N=97)	P-Value
Low Birth Weight <2500 grams	16 (18 %)	2 (2%)	<0.001
Very Low Birth Weight <1500 grams	4 (5 %)	1 (1%)	0.19
Preterm Delivery	16 (18 %)	7 (7.2%)	0.027
Newborn Death	2 (2 %)	1 (1%)	0.60
NICU Admission	11 (13%)	7 (7%)	0.20
Any Serious Adverse Event	33 (37.9%)	24 (24.7%)	0.057

Although two large efficacy studies in pregnant smokers did not show an increase in quit rates with NRT, they did show an increase in birth weight and improved infant outcomes. The lack of efficacy in the trial by Wisborg et al. (7) is likely due to poor medication compliance. In our study (1), the lack of efficacy on quit rate could be due to the lower efficacy of nicotine gum compared to other NRTs, compounded by the inadequate daily use of the gum by participants. Nausea (a common complaint in pregnancy and a common adverse effect of nicotine gum) may have reduced the rates of gum use. There was an increase of 20% in the prevalence of nausea in the NRT group vs. a 2% decrease with placebo ($p=0.019$), suggesting that nicotine gum has limited clinical utility in this population. ***Although NRT has not been shown to enhance quit rates in pregnant women, it has reduced the number of CPD and yielded better infant outcomes. Placebo-controlled RCTs are needed to test the safety and efficacy of each first-line medication in pregnant smokers.***

A.2.c.Rationale for the choice of the nicotine inhaler for smoking cessation during pregnancy: Any of the first-line therapies could reasonably be used for smoking cessation in pregnancy. In the absence of clear guidelines, we have relied on the consensus of our study obstetricians that it is preferable to

withdraw pregnant women from a drug that they are already taking (i.e., nicotine) than to add a new drug with unknown effects (e.g., varenicline). Moreover, many women in our previous study were already taking antidepressants. Adding bupropion (because of drug interactions) or varenicline (rare risk of neuropsychiatric effects) in these individuals is not desirable. We chose to study an intermittent nicotine delivery system, rather than a continuous delivery system because it limits nicotine exposure, can be used to manage smoking urges, and allows the dose of nicotine to be titrated by the patient [6]. This choice is consistent with guidelines [2,38] and expert recommendations [37] on the optimal approach to smoking cessation treatment in pregnancy.

Of the intermittent replacement products, the inhaler and nasal spray have better efficacy than the gum, and nausea is not a common adverse effect of either. We chose to use the inhaler because: 1) it provides some of the sensory and ritualized components of smoking; 2) it is a preferred treatment among smokers sampling intermittent NRT products [39]; 3) with *ad libitum* use it produces nicotine concentrations that are relatively low (i.e., 6-9 ng/mL) and overall nicotine exposure is approximately 60% of that with smoking [6, 40]; and 4) it is well accepted by low-income, non-pregnant smokers who attend the smoking cessation clinic at Hartford Hospital, a population similar to the pregnant women to be examined in this study. Although the nasal spray enhances quit rates in non-pregnant smokers, it is difficult for patients to use, and is associated with nasal adverse effects, which can worsen nasal stuffiness, a common symptom of pregnancy [41].

A.2.c.Pilot study: We chose the nicotine inhaler as the pharmacotherapy to be examined in pregnant smokers because of theoretical reasons (intermittent delivery system, good efficacy in non-pregnant smokers, adverse event profile in non-pregnant smokers). Our pilot study results confirm that the nicotine inhaler is a reasonable option for smoking cessation during pregnancy and allowed us to better characterize the dosing regimen for smoking cessation in light smokers.

Six women received open label use of nicotine inhaler for a 4 week pilot study. Subjects were approximately 26.8 years old (range 22-38), and 67% were minorities (two Black, 2 Hispanic). Subjects smoked a mean 6.4 (range 5-10) CPD at study entry, and were smoking for approximately 10 years. Two subjects were on methadone maintenance, and one recently completed treatment for marijuana abuse. Three subjects had a previous history of adverse pregnancy outcome (2 spontaneous abortion, 1 stillbirth). Subject retention rate was 83% (one subject dropped out for housing issues). Mean cartridge use was 2 (range 1-4) inhalers per day. There was a mean (SD) reduction of 5.7 (2.3) CPD from baseline to 4 weeks, and 3 of the 6 women enrolled quit smoking (1 woman who dropped out was counted as smoking). Mean percent nicotine replacement (cotinine value at 2 weeks/baseline value x 100) was 66%. All subjects rated the statement "The inhaler relieves urges to smoke," either "definitely true" or "very definitely true." In response to the statement "I would use the nicotine inhaler as a method to quit smoking, one person chose 5 (probably), and the rest chose 6 "definitely" or 7 "very definitely".

Adverse effects: On at least one visit, 4 subjects reported mouth/throat irritation with inhaler use (3 were of mild and 1 was of moderate severity). This resolved in all subjects with continued use and instruction to take shallower breaths. Two subjects complained of headache, which resolved with shallower puffs on the inhaler. One subject complained of mild nausea, which she thought was unrelated to inhaler use.

Our pilot data show that the nicotine inhaler is a good choice for smoking cessation during pregnancy. Study subjects used it effectively and reported it to be acceptable. Percent nicotine replacement with ad libitum use is in line with that observed in non pregnant smokers (approximately 60%)[6]. Fifty percent of individuals quit smoking. Side effects were minimal and were reduced when subjects were instructed to take shallower breaths. The proposed study (described in methods) builds on the existing literature by examining the safety and efficacy of the nicotine inhaler for smoking cessation during pregnancy.

A 3. Importance of Measuring Biomarkers: We will evaluate specific biomarkers of smoking-related harm during pregnancy, which may help explain how smoking cessation or reduction increases birth weight and gestational age. Although biomarkers of chemical exposure (e.g., exhaled CO, cotinine, anabasine/anatabine, thiocyanate) can be used to measure tobacco exposure, we believe that it is scientifically important to carefully evaluate potential biomarkers of smoking-related harm (i.e., physiological change biomarkers), because these may help to elucidate the mechanisms by which tobacco cessation/reduction increases gestational age and birth weight [46]. Although many biomarkers have been theorized to contribute to cardiovascular disease, pulmonary disease, or cancer in non-pregnant smokers, none have been shown to predict clinical outcomes, because of the length of time it takes to develop various diseases [46]. Pregnancy is a unique situation that lends itself to the examination of biomarkers of tobacco risk, because of the rapid fetal growth that occurs during a 9-month period.

In this study we will examine two biomarkers of interest [high sensitivity C-reactive protein (a marker of inflammation), and soluble intracellular adhesion molecule (sICAM), a measure of inflammation and endothelial function] as potential mediators of tobacco-related harm. We chose these biomarkers because they: 1) have been implicated in medical harm (particularly vascular disease) in non-pregnant smokers [46, 47], which may be applicable to pregnancy because the placenta is highly vascularized; 2) are associated with tobacco use, change with cessation, and are dose-related to smoking [46, 48]; and 3) have been associated independently with birth weight or gestational age in pregnant women who do not smoke (suggesting biological plausibility). In pregnancy, increased systemic inflammation (as evidenced by increased C-reactive protein concentration) has been linked to preterm delivery [49], low birth weight [50], and placental accidents and stillbirths [51]. Additionally, inflammation likely contributes to the endothelial dysfunction observed in smokers. Extensive endothelial damage has been identified in the umbilical arteries from placentas obtained from smoking mothers [52, 53], and may contribute to the reduced placental blood flow, increased thrombosis and platelet aggregation, and reduced fetal growth associated with maternal smoking. Indeed, sICAM, a cell surface adhesion molecule that is increased in inflammatory states, is elevated in pregnant smokers [48] and is linked to fetal growth restriction [54] and preterm delivery [55]. Based on the aforementioned data, both sICAM and C-reactive protein are potentially high-yield biomarkers that may mediate the relationship between tobacco exposure and LBW and preterm delivery. An examination of the mechanisms underlying the longer gestational age and greater birth weight that we saw in our prior study [1] is important, given the clinical significance of these outcomes on infant morbidity and mortality [13].

Evidence that these biomarkers are mediators of pregnancy outcomes that are affected by smoking has important implications for other pharmacotherapy studies in pregnant smokers by providing surrogate measures of potential risk [46] or in studies of reduced-exposure products (e.g., e-cigarettes, smokeless tobacco) that may be used by pregnant women. Since the FDA has recently been authorized to regulate tobacco products [56] there is likely to be heightened interest in biomarkers of tobacco product risk, particularly in vulnerable populations.

3. Hypotheses, aims and objectives:

Hypothesis 1:

We hypothesize that the nicotine inhaler compared to placebo inhaler will double the 7-day point prevalence abstinence rates (confirmed by exhaled CO) at 32-34 weeks gestation and will reduce the number of cigarettes smoked per day (CPD).

Aims / objectives 1:

To examine the efficacy of the nicotine inhaler compared to a matched placebo for smoking cessation and reduction among pregnant smokers.

Hypothesis 2:

a) The nicotine inhaler will yield lower cotinine concentrations than placebo at 32-34 weeks gestation.

b) Infants born to mothers in the NRT group will have higher birth weights and greater gestational age than infants born to mothers randomized to placebo. 2c) Fewer nicotine-treated subjects will deliver a low birth weight (<2500 grams) or a preterm (<37 weeks) infant than those in the placebo group.

Aim/Objective 2:

To compare the nicotine inhaler with placebo on safety measures which include a) overall nicotine exposure (i.e., serum cotinine) and b) birth outcomes (i.e., birth weight and gestational age).

Hypothesis 3: Pregnant women who are heavier smokers (i.e., ≥ 10 cigarettes/day) will be less able to quit with behavioral treatment alone than lighter smokers and the inhaler will increase cigarette abstinence more in heavier smokers.

Aim/Objective 3: To identify factors that determine which women benefit most from the use of nicotine inhaler for smoking cessation during pregnancy

Hypothesis 4: We hypothesize that birth weight will be negatively correlated with CPD and exhaled CO at the end of pregnancy, and that smoking cessation or reduction in the third trimester will explain the effect of treatment group on birth weight. We will also explore the interrelations among birth outcomes, tobacco exposure, and other promising biomarkers.

Aim/Objective 4: To explore mechanisms by which the nicotine inhaler increases birth weight and gestational age.

4. Study Design & Procedures:

Study design: This is a randomized, double blind, placebo-controlled trial of the safety and efficacy of the nicotine inhaler in combination with behavioral counseling for smoking cessation during pregnancy. A total of 360 pregnant smokers will receive nicotine or placebo inhaler medication (1:1 ratio) for 6 weeks followed by a 6-week taper, with double-blind treatment conditions maintained throughout the study. Smoking cessation counseling and medication will be provided by a nurse at each ambulatory clinic. Nurses will be closely supervised by a psychologist with extensive expertise in smoking cessation (Dr. Dornelas), an obstetrician (Dr. Griswold or Dr. Sankey), and Dr. Oncken.

Overview of the behavioral intervention: The behavioral intervention, which will be utilized in both arms of the proposed study, exceeds many of the augmented interventions described in the USPHS guidelines [38]. The behavioral counseling will include a 35-minute counseling sessions at each of the first two visits, and 10 minutes of smoking cessation counseling at subsequent visits, delivered by the study nurses.

Overview of pharmacotherapy intervention: We will administer a 6-week course of therapy, consistent with instruction on the package insert. Dosage recommendations are based on the literature and on our pilot data, and will vary according to the level of maternal smoking. Pfizer Pharmaceuticals has agreed to supply us with nicotine inhaler and placebo treatments (see letter of support). To enhance compliance and to confirm patient reports and proper inhaler use, subjects will be asked to keep a daily diary of the number of cartridges used and to return all cartridges at the next study visit. Subjects will be instructed to bring medication and empty cartridges to next visit when they receive their reminder telephone call regarding upcoming appointments. For convenience, subjects will receive a plastic container to transport study drug. At Visit 5 (6 week visit), patients will be instructed on an individualized basis to taper their use over the next 6 weeks. If a study subject does not quit smoking

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during the first 6 weeks of active treatment, it is unlikely that she will quit during the medication taper. Consequently, at visit 5 (6 week visit), subjects who have not quit smoking (7 day point prevalence abstinence confirmed with exhaled carbon monoxide measurement) will be discontinued from medication treatment and reminded to return all study medication at the next scheduled visit.

Recruitment: We will recruit 360 pregnant women from patients seeking care at the Women's Health Ambulatory Clinic located at Hartford Hospital (HH) or the Wesson Women's & Infants' Unit at Baystate Medical Center (BMC) and Community Health Services (CHS) in Hartford. Study visits will occur at either Hartford hospital (referrals from HH clinic, CHS, or the surrounding greater Hartford area) or Baystate Medical Center (referrals from Wesson Women's Clinic and Baystate Maternal Fetal Medicine Clinic). Baystate will also accept referrals from several Baystate Health Medical practices in other locations, including Baystate Midwifery and Women's Health (3300 Main Street); Baystate Wesson Women's Group (3300 Main Street); Baystate Mary Lane (Ware, MA), Women's Health Associates and Baystate Wing (Ludlow, MA and Palmer, MA). Study visit will occur at either Baystate Medical Center or at one of the above locations, depending on the subject's preference.

Study staff will also accept referrals from each of the practice locations noted above. In addition, potential participants may refer themselves to the study by contacting study staff directly or by leaving their contact information on the study voicemail. These individuals will be contacted to determine if they are interested in participating in the study. For the convenience of our subjects, those who receive their prenatal care at a Baystate practice location outside of Baystate Medical Center will be offered the option of receiving study visits at their prenatal care location. The Clinical RN Study Coordinator will travel to the practice location to conduct study visits. Study drug will be dispensed at these visits in the same manner as it is dispensed at Baystate Medical Center. Study drug will be signed out from Baystate Investigational Pharmacy prior to the study visit and will be transported by the study RN to the site. The study drug will remain in the RN's possession until it is dispensed to the subject per the protocol; drug dispensing will be documented in the subject's record as well as in the study drug accountability log per protocol.

Pregnant smokers will first be identified by clinic personnel and referred to our recruiter after expressing an interest in study participation. Study sites will also utilize direct mailings and Internet advertising for recruitment purposes. Study personnel at Baystate will review CIS to assess potential eligibility of women identified in the daily appointment report of all women scheduled for OB appointments at Wesson Women's Clinic, Baystate Maternal-Fetal Medicine, Baystate Midwifery and Women's Health, Baystate Wesson Women's Group, Baystate Mary Lane, and Baystate Wing. Women identified as potential participants will be approached to determine if they are interested in participating in the study. Subjects who are eligible and wish to participate will be asked to provide written informed consent before any other information is obtained. Potential subjects 16 and 17 years of age enrolled in CT will require parental consent. After the subject gives informed consent, basic inclusion/exclusion criteria will be assessed. If there are questions regarding the appropriateness of the subject's study participation, eligibility will be reviewed by the study nurse and physician prior to randomization. Given the young age of the population, a proportion will be adolescent, which is responsive to the NIH policy concerning pediatric populations.

Screening Procedures and who will perform them: A study recruiter will accept study referrals, and perform screening procedures. If the study recruiter not available to speak with a referred potential subject, the study nurse or physician may obtain consent and perform screening procedures.

Screening procedures will include consent signing, assessing inclusion/exclusion criteria, and other contact information. The following questionnaires/assessments will be obtained:

1. **Demographics:** Age, education, race/ethnicity, income, and type of insurance (public or private),
 2. **Smoking history:** We will inquire about past and current smoking, including CPD currently and prior to pregnancy, intention to quit, partner smoking, motivation to quit and number of years of smoking [20, 71]. We will also evaluate prior use of medication to stop smoking and other drugs, including symptoms of other drug abuse or dependence. Smoking social networks will be assessed with items on the smoking status of partner and friends, the number of household smokers, perceived support for staying abstinent and the composition of the household (age and relationship to the subject) [72]. The Fagerstrom Test for Nicotine Dependence [70], a 6-item scale (internal consistency = 0.61), will be used to measure dependence on nicotine.
 3. **Screening medical and obstetrics history** will include the number of pregnancies, previous pregnancy outcomes (preterm, term, living, abortions), and information on any current pregnancy problems or underlying medical disorders (e.g., diabetes or HIV infection). Current and past drug abuse history will be recorded. Ongoing medications will be recorded.
 4. **Vital signs** (blood pressure, pulse) and **weight** will also be recorded.
 5. **PHQ:** We have chosen to identify major psychopathology using the PRIME-MD Patient Health Questionnaire [74]. This questionnaire consists of nine questions that screen for depression. Each item yields a score of 0-3, and the highest possible total score for all items is 27. The scale can be used longitudinally to identify trends in depressed mood. Subjects with evidence of suicidal ideation or any other severe, acute psychiatric symptom (e.g., psychosis) will be excluded from the study. Subjects who answer “more than half the days” to 5 or more items will be excluded from the study. Since the questionnaire relies on patient self-report, all responses will be verified by the principal investigator, if a subject answers “more than half the days” to 5 or more items to confirm exclusion is warranted.
 6. **Self-efficacy questionnaires:** Evaluates confidence to resist smoking across a number of different situations [60]. The scale yields a total score, as well as subscores for positive & negative affect situations, and habit/craving items. This scale has been a strong predictor of smoking outcomes in previous studies [73].
 7. **Exhaled carbon monoxide measurement.** Subjects will be asked to blow into a machine that measures CO in parts per million (ppm). Levels <9 ppm are consistent with cigarette abstinence [69].
 8. **Urine sample:** A urine sample will only be collected at BL, V2, V5, and V6 and analyzed only if serum can not be obtained. Urine will be tested using the NicAlert method.
- The screening visit is expected to take 1.5 hours.** The participant will be given a handout to record cigarette intake prior to subsequent study visits.

Study Procedures and who will perform them:

Baseline: Eligible subjects scheduled to return for a baseline (i.e. randomization) visit approximately 1 week after screening (+ 14 Days). The study nurse will review the patient’s medical history and confirm current medical and pregnancy history. She will discuss each case with the study obstetrician (at the performance site) who will sign off on entry of subject into the study.

1. **Randomization assignment:** As previously noted randomization will be 1:1 for nicotine inhaler or placebo assignment. To ensure comparability of subjects in the treatment groups, we will employ urn randomization, a probabilistic balancing procedure that assigns patients to conditions so that groups are balanced on key variables [57]. Key variables that we would like to balance groups on include history of preterm delivery (yes/no), gestational age at study entry (<19 weeks vs. ≥19 weeks), and number of CPD (<10 vs. ≥ 10).

The nurse will fax key variables for a given subject to the research pharmacist at UCONN who will enter these variables into a specially developed computer algorithm by that is

the basis for the urn randomization procedure. In this way, treatment groups will be comparable on important features that may influence treatment outcome. Once the pharmacist enters these variables, the computer assigns a treatment assignment. The pharmacist will communicate with the study nurse (by fax or e-mail) which medication box # to dispense to the subject.

2. **Maternal blood draw** (approximately 15 cc): Venipuncture will be performed using standard sterile blood drawing techniques by trained personnel. Serum will be separated on site and stored at -20 degrees C on at least a biweekly basis until transfer to UCHC where it will be stored at -70 C. Samples will be measured for cotinine, the major metabolite of nicotine, and a reliable measure of overall nicotine intake. Cotinine will be measured by GC/Mass Spectrometry at Yale University. UCHC Core Lab will ship transport tubes to Yale after subjects' Week 2 visit. If the subject does not come to Visit 2, the blood will be obtained at the next scheduled visit. Serum will also be measured for hydroxycotinine/cotinine ratio, the rate at which nicotine is metabolized. Samples will be shipped in compliance with DOT/IATA regulations (dry ice, FedEx Overnight Express, etc.). The results will be emailed to the P.I. and the study coordinator at each site. Serum will be measured for high sensitivity C-reactive protein (Siemens Medical Diagnostics, Los Angeles CA) by solid phase chemiluminescent immunometric assay and sICAM (R&D systems, Minneapolis, MN) measured by sandwich EIA in the GCRC core laboratory. If possible, this blood draw will be incorporated with other routine prenatal blood draws.
3. **Urine sample:** Urine will only be used as a backup for cotinine if necessary.
4. **Exhaled carbon monoxide (CO) measurement and Nicotine Use survey** (which assesses any smoking last seven days and since the last study visit and use of other smoking cessation aids)
5. **Vital Signs** (blood pressure and heart rate) and **Weight** will be obtained.
6. **Adverse Effects Inhaler:** Subjects will rate potential adverse effects (cough, throat irritation, rhinitis, and mouth irritation, which have been noted in other nicotine inhaler studies [6, 40, 66]) on a 4-point scale: 0=absent, 1=mild, 2=moderate, and 3=severe. Other AE's will also be recorded and severity rated. This will be done before the subject is administered treatment so we have a baseline to compare other visits.
7. **Concomitant Medication:** Subjects will be asked about their current medication use, including any prescription medication, over the counter medication, supplement, and/or vitamins.
8. **The Minnesota Nicotine Withdrawal Scale (MNWS)** measures symptoms of tobacco withdrawal on a scale of 0 (not present) to 4 (severe) [24]. We will calculate a total score and a score excluding craving to evaluate withdrawal symptoms during cessation.
9. **Release of Information:** A release of information will be obtained at the baseline visit so the study physicians are able to obtain delivery records if the participant will deliver at a hospital other than HH or BMC.
10. **Counseling:** There are 4 primary goals in the initial counseling session: (1) establishing a rapport with the patient, (2) functional analysis of smoking including a review of self-efficacy in various situations, (3) increasing motivation and confidence to quit smoking (using techniques described in the manual), (4) helping the patient to set and prepare for a quit date.

The study nurse provides 35 min of smoking cessation counseling. Subjects will be given "Need Help putting out that Cigarette?" a booklet available for purchase through the American College of Obstetrics and Gynecology. This booklet is written in English or Spanish, is at a 6th grade reading level, provides information about smoking in pregnancy, and outlines steps to prepare to quit and stay quit during pregnancy. The nurse will use responses to the self efficacy questionnaire and diary to help subjects recognize high-risk situations and develop specific strategies to deal with them. The treatment manual describes four primary sources that influence

self-efficacy (1) prior experience, (2) modeling or vicarious experience, (3) positive social persuasion and (4) somatic/physiological and/or emotional states [3] and specific techniques that can be used to address self efficacy in each of these domains. Multiple studies have established that the use of these techniques reliably increases self-efficacy across a variety of addictive behaviors [4].

The nurse will teach participants to use the inhaler properly (see below on instructions), and have them try it under supervision. Subjects asked to identify a quit date (within the next week), and are prepared for this quit date by the study nurse. Active inhaler or placebo dispensed with instructions to begin regular use on the quit date.

- 11. Dispense Study Drug/Usage Instructions:** Because there is no known safe level of smoking, the goal of treatment will be total abstinence. Subjects will be informed that the nicotine inhaler is most effective if used regularly and that they should use the medication for breakthrough cravings, as needed. We will instruct subjects that each use of the inhaler should consist of puffing on it frequently up to a 20-30 minute period (as in previous studies) [66]. As a rough guide, subjects will be informed that 80 puffs on the inhaler (3-4 puffs per minute for 20-30 minutes) delivers a dose of nicotine that is approximately equal to one that would be delivered by 1 cigarette (i.e., 1 mg of nicotine). The study nurse will demonstrate for the subject the proper inhaler use.

Subjects will be instructed to begin using the inhaler on their quit date. Our choice of dosage is aimed at relieving withdrawal symptoms, so we will encourage heavier smokers to use more inhaler cartridges than lighter smokers. Subjects who smoke ≥ 10 CPD will be instructed to begin with 4-12 cartridge inhalers/day, which is consistent with other inhaler studies that have recommended a minimum use of 2 inhalers per day [67], or 4 inhalers per day [66], although use of at least 6 inhalers per day was recommended by others [40], including the package insert. However, clinical efficacy is observed with use of at least 4 cartridges per day, which is the minimum dose we will recommend for women who smoke ≥ 10 CPD. Women who smoke 5-9 CPD will be instructed to begin by using 1-4 cartridge inhalers/day, based on an estimated 1-2 mg of nicotine per cigarette, with each cartridge inhaler estimated to release 4 mg of nicotine [6]. Use of 1-4 cartridges/day by 4 light smokers in the pilot study resulted in 62% nicotine replacement. Dosage adjustments will be made in response to withdrawal symptoms and cotinine levels. We will monitor cotinine levels after the women have used the inhaler for 2 weeks. Subjects will be notified by the research study nurse if there is a significant increase in cotinine above baseline values while smoking (see DSMP for cotinine monitoring). In our previous study [1], this approach worked well previously to ensure that cotinine levels were not excessive.

Nurse will distribute a 2 week supply of study medication. The participant will be given a handout to record inhaler use and any concomitant smoking prior to subsequent study. The baseline visit will take 1.5 hours.

- 12. Phone call (On Target Quit Date):** Subjects will receive a telephone call on their quit date (+/- 2 days) to discuss cognitive behavioral strategies identified for high risk situations, inhaler use, and to provide support for smoking cessation.
- 13. Reminder Phone Calls:** Subjects may receive reminder phone calls and/or text messages via a secure device based on participant preference, regarding appointment dates and times. They will also be instructed to return study medication, when appropriate.
- 14. Missed Visits:** Since this population has a high “no show” rate for assigned visits, some procedures will need to be adjusted for safety purposes and to achieve research goals.

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Visit 1: Subjects seen approximately 1 week (+/- 4days) after their quit date to assess adverse effects and progress in smoking cessation. At this visit, the nurse administers behavioral counseling (35 minutes) and assesses medication usage. The study coordinator will administer all assessments.

1. Vital signs and weight
2. Exhaled CO measurement
3. Nicotine Use Survey
4. Questionnaires: MNWS
5. Adverse Effects Inhaler & Adverse Events
6. Concomitant Medication
7. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
8. Counseling: The second counseling session is scheduled 1 week after the quit date. The primary focus of this session will be to assess reactions to the initial session, smoking status, and the effectiveness of the intervention, and to discuss strategies to deal with smoking urges and tobacco withdrawal symptoms. Subsequent sessions will focus on achieving or maintaining abstinence, increasing self-efficacy, skills training (depending on the patient's smoking status), and providing support.

This visit will take 45 minutes.

Visits 2 (2 weeks after the quit date +/- 4 days). The following items will be assessed by research nurse.

1. Vital signs and weight
2. Exhaled CO measurement
3. Maternal Blood draw (15 cc) If possible, this blood draw will be incorporated with other routine prenatal blood draws. Will collect urine as backup.
4. Nicotine Use Survey
5. Questionnaires: MNWS, PHQ
6. Adverse Effects Inhaler & Adverse Events
7. Concomitant Medication
8. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
9. Dispensement: We will dispense a 2 week supply of study medication, if needed.
10. Counseling (10 Minutes): Counseling will focus on achieving or maintaining abstinence (set another quit date if necessary), increasing self-efficacy, skills training (depending on the patient's smoking status), and providing social support, and using inhaler to combat urges to smoke).

This visit will take 45 minutes. After the session the nurse will send the two maternal serum samples for cotinine analyses. If the visit 2 sample exceeds that of baseline by 40%, the study nurse will call the patient and advise a decrease in inhaler dosage that will be recommended by Dr. Oncken.

Visit 3 (3 weeks after the quit date +/- 4 days). The following items will be assessed by research nurse.

1. Vital signs and weight
2. Exhaled CO measurement
3. Nicotine Use Survey
4. Assignment: To examine whether the blinding was successful, subjects will be asked which treatment they think they received (active or placebo inhaler).
5. Adverse Effects Inhaler & Adverse Events
6. Concomitant Medication

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7. MNWS Questionnaire
8. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
9. Counseling (10 Minutes): Counseling will focus on achieving or maintaining abstinence (set another quit date if necessary), increasing self-efficacy, skills training (depending on the patient's smoking status), and providing social support, and using inhaler to combat urges to smoke).

This visit will take 45 minutes.

Visit 4 (4 weeks after the quit date +/- 4 days). The following items will be assessed by research nurse.

1. Vital signs and weight
2. Exhaled CO measurement
3. Nicotine Use Survey
4. Questinnaires: MNWS
5. Adverse Effects Inhaler & Adverse Events
6. Concomitant Medication
7. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
8. Dispensement: We will dispense a 2 week supply of study medication, if needed.
9. Counseling (10 Minutes): Counseling will focus on achieving or maintaining abstinence (set another quit date if necessary), increasing self-efficacy, skills training (depending on the patient's smoking status), and providing social support, and using inhaler to combat urges to smoke).

This visit will take 45 minutes.

Visit 5 (6 weeks after the quit date +/-10days). The following items will be assessed by research nurse.

1. Vital signs and weight
2. Exhaled CO measurement
3. Nicotine Use Survey
4. Questionnaires: MNWS, PHQ
5. Adverse Effects Inhaler & Adverse Events
6. Concomitant Medication
7. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
8. Taper: (Discuss scheduled taper with goal of being off medication by 6 weeks for subjects who are abstinent from cigarette smoking (no smoking last 7 days confirmed with exhaled CO)
9. Maternal Blood draw (15cc). If possible, this blood draw will be incorporated with other routine prenatal blood draws. Will collect urine as backup.
10. Counseling (10 Minutes): Counseling will focus on achieving or maintaining abstinence (set another quit date if necessary), increasing self-efficacy, skills training (depending on the patient's smoking status), and providing social support, and using inhaler to combat urges to smoke).
11. Serum will be sent for cotinine analysis only if the nurse identifies that the subject has significantly changed her smoking and/or inhaler use patterns (see DSMP for cotinine monitoring).

This visit will take 45 minutes.

Visit 6 (32-34 weeks gestation). The following items will be assessed by research nurse.

1. Vital signs and weight
2. Exhaled CO measurement

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3. Nicotine Use Survey
4. Questionnaires: MNWS, PHQ
5. Adverse Effects Inhaler & Adverse Events
6. Concomitant Medication
7. Inhaler usage: We will collect used cartridges from patient and review diary of inhaler useage.
8. Maternal Blood Draw (15 cc) If possible, this blood draw will be incorporated with other routine prenatal blood draws. Will collect urine, if necessary.
9. Counseling (10 Minutes): Counseling will focus on achieving or maintaining abstinence (set another quit date if necessary), increasing self-efficacy, skills training (depending on the patient's smoking status), and providing social support, and using inhaler to combat urges to smoke).
10. Serum will be sent for cotinine analysis only if the nurse identifies that the subject has significantly changed her smoking and/or inhaler use patterns (see DSMP for cotinine monitoring).

This visit will take 45 minutes.

Birth outcomes: the research nurse or study coordinator will collect birth outcomes by chart review. Permission to conduct chart review for labor and delivery records will be included in the informed consent form. Information to be collected includes: Apgar scores, birth weight, infant sex, gestational age, head circumference, NICU admission, and infant length of stay. Other rare events associated with tobacco use during pregnancy and maternal medical conditions will also be recorded. Time to collect birth outcomes is estimated at 30 minutes.

Visits 7 & 8: 1- and 6-month postpartum follow-up visits will be completed to assess smoking relapse. We have chosen these time points because the majority of post-partum relapses occur during this period [18]. To reduce subject burden visit 7 will be done by phone. If unable to contact participant, the chart will be reviewed for smoking status.

Visit 7 (1 month postpartum +/- 7 days). The following items will be assessed by research nurse or study coordinator via a telephone call. Nicotine Use survey

1. Counseling to encourage abstinence postpartum

Visit 8 (approximately 6 months postpartum +/- 14 days). The following items will be assessed by research nurse or study coordinator.

1. Nicotine Use survey
2. Exhaled CO measurement if visit is attended
3. Counseling to encourage abstinence postpartum

As a back-up plan, study staff (not R.N.) will perform study procedures at visits that do not require study drug dispensement (Visits 1, 3, and 6). In this instance, the R.N. will complete the behavioral counseling via the telephone.

Sample size and justification:

Aim 1: Based on our nicotine gum study, we estimate that the quit rate will be 14.9% in the placebo group and 26.9% in the nicotine inhaler group (consistent with an odds ratio of 2.1 obtained in meta-analyses of inhaler effects in non-pregnant smokers [2]. Thus, 360 women (180 in each of the treatment group) would yield power of 0.80 to detect a significant difference using a two-tailed test and $\alpha=0.05$. Thus, 360 women (180 in each of the treatment group) would yield power of 0.80 to detect a significant difference using a two-tailed test and $\alpha=0.05$.

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Aim 2: Using data from our completed study, a total of 226 subjects will yield power=0.80 (two-sided $\alpha=0.05$) to detect a difference of 100 ng/mL (SD=360) in the reduction in cotinine concentrations between groups. In our completed study (N=194), we observed a difference in birth weight of approximately 300 grams (SD 607), which was highly significant. Assuming a comparable effect size, we will have more than adequate power to detect birth weight differences between groups. Thus, our sample size of 360 is more than sufficient for this aim.

Aim 3: In our completed study, the effect of nicotine gum appeared to depend on cigarettes per day during the pretreatment period. For light smokers, the cessation rates were 18% and 21% for the control and nicotine groups, respectively, while for heavy smokers the rates were 0% and 15%, respectively. Since a similar effect in a sample of 150 women would provide power=0.80, using a two-sided $\alpha=0.05$, our proposed sample of 360 pregnant smokers will provide more than adequate power to detect the effect.

Aim 4: is exploratory and no sample size was calculated.

Explain on what basis it is reasonable to assume that the sample size will be obtained:

Recruitment will take place over 39 months, requiring enrollment of approximately 9 subjects per month. In our previous study, we had an on-site recruiter at each site (Baystate and Hartford Hospital) and were able to screen 3 pregnant smokers and enroll 2 subjects/week (i.e., 1 subject/site). We will also recruit from CHS in Hartford, where we expect to recruit 1 subject/month. Recruitment sites will be provided with 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 recruit through newspapers and maternity magazines. Based on our history of recruitment, we are confident that we can reach the proposed recruitment goal.

Subject characteristics:

- Age: at least 16 years of age
- Ethnicity: **Hispanic and non-Hispanic. All race and ethnic groups will be eligible**
- Gender: F
- Other characteristics - (e.g. primary language etc.): **English or Spanish speaking**

Inclusion Criteria:

- a) smoking at least 5 CPD for the preceding 7 days
- b) previous attempt to quit smoking during pregnancy by self report
- c) 13-26 weeks gestation
- d) at least 16 years of age
- e) able to speak English or Spanish;
- f) intent to carry pregnancy to term; and
- g) stable residence

Exclusion criteria:

- a) current drug or alcohol abuse or dependence (other than methadone maintenance)
- b) twins or other multiple gestation
- c) unstable psychiatric disorder
- d) unstable medical problems (e.g., pre-eclampsia, threatened abortion, hyperemesis gravidarum)
- e) known congenital abnormality.

Describe length of subject's participation in the study including number of visits, frequency of visits, and length of visits:

The subject will be in the study from the time of enrollment (13-26 weeks gestation) until 6 months after delivery. Each subject will have 10 visits. The screen and baseline visit are each 1.5 hours long. The remaining visits are approximately 45 minutes long.

Methods of Data Collection and Types of Data to be collected (may refer to attached surveys/ forms etc.)
See Attached surveys

Method(s) of data analysis:

Specific Aim 1: To compare the efficacy in pregnant smokers of the nicotine inhaler or matching placebo for smoking cessation and reduction in pregnant smokers We will first examine variation in the main outcome (7 day PPA rates at 32-34 weeks gestation) by treatment site using the intraclass correlation coefficient. If there is a difference by site, it will be used as a nesting factor in a generalized estimating equations logistic model. At the end of patient follow-up, the difference in the proportion of subjects who successfully quit smoking will be calculated along with a 95% confidence interval for the “true” difference between treatment groups. To evaluate whether randomization was effective, summary statistics for patient characteristics in the two study arms will be compared. If there is an imbalance in patient characteristics, statistical adjustment will be used to ensure that the initial results were not biased by those imbalances.

We will use a linear mixed model to evaluate the effects of the nicotine inhaler on smoking reduction or exhaled CO from baseline first to 6 weeks and then to 32 weeks gestation. Prior to these analyses, the distribution of the dependent variables, number of CPD (and exhaled CO), will be examined for normality and outliers and transformations will be performed if necessary. Treatment group and visit will be fixed factors and the intercept will be random. The model will also include a treatment-by-time interaction to test whether, over time, the number of CPD changes differentially by treatment group.

Specific Aim 2.a: To compare effects of the nicotine inhaler with placebo on overall nicotine exposure (i.e., measured as serum cotinine), and birth outcomes [i.e., birth weight, gestational age, % of subjects who deliver a LBW (<2500 g) or preterm (<37 wk gestation) infant]. We will use a linear mixed model (see above) to determine whether cotinine concentration changes differentially over time by treatment group.

Specific Aim 2.b: Birth Outcomes. Mean birth weight will be compared for treatment groups using a two-sample t-test, or analysis of covariance if necessary to adjust for imbalances in patient characteristics. We will also compare the percentage of subjects in each group who deliver an infant of LBW (1500-2500 g) or preterm delivery using chi square or logistical regression.

Specific Aim 3: To determine which subjects benefit most from NRT, we will use logistic regression to examine the following predictors of treatment response (i.e., smoking cessation at 6 or 32 wks

gestation): pretreatment CPD, FTND score, perceived stress, motivation to quit, self-efficacy, treatment group, and the interaction of treatment group and the other independent (i.e., potential moderator) variables. **Analyses:** First, we will use a stepwise procedure to choose predictor variables and interaction terms that are significant ($\alpha=0.05$). A significant interaction between treatment group and other variables (e.g., \pretreatment CPD) implies that the regression coefficients for this variable are not homogeneous with respect to the efficacy of the medication. The Johnson-Neyman procedure [79], which yields values of the continuous moderator variable at which the treatment groups differ significantly on the dependent variable, will be used to determine the “break point” nicotine inhaler efficacy. In our completed study[1], the effect of nicotine gum appeared to depend on CPD during the pretreatment period. For light smokers, the cessation rates were 18% and 21% for the control and nicotine groups, respectively, while for heavy smokers the rates were 0% and 15%, respectively. Since a similar effect in a sample of 150 women would provide power=0.80, using a two-sided $\alpha=0.05$, our proposed sample of 360 pregnant smokers will provide more than adequate power to detect the effect.

Mediational analyses: Measures of nicotine withdrawal, depressive symptoms, and perceived stress measured at baseline and at each study visit will serve as potential mediators. Specifically, we expect that the nicotine inhaler will result in a greater reduction in nicotine withdrawal symptoms than placebo, and that these variables will partially mediate the effects of treatment. Tests of mediation using the Mplus statistical package [80], which allows for missing data, will provide evidence of a causal link between treatment, the mediator variable(s), and the outcomes.

Specific Aim 4: To explore mechanisms by which the nicotine inhaler increases birth weight and gestational age. Based on the results of our completed study [3] and another NRT trial [7], we anticipate that offspring born to women in the inhaler group will have a higher birth weight and gestational age than those in the placebo group. If NRT increases birth weight, potential mediators of this effect will be explored. Measures of tobacco use (cigarettes per day, and exhaled co) and 7 day point prevalence abstinence at each study visit will serve as potential mediators. Specifically, we expect that the nicotine inhaler will result in cessation or a greater reduction in CPD or exhaled CO, and that these variables will partially mediate an increase in birth weight. We will use a Mplus statistical package to the perform mediational analyses [80]. The same analytic approach will be used separately to examine gestational age (in wk).

Depending on whether smoking cessation or reduction mediates the effect of NRT on birth weight, the appropriate variable will be used a predictor variable in an additional mediational model that examines potential biomarkers (**C-reactive protein or sICAM**) as mediators of birth weight or gestational age. Specifically we will test with Mplus statistical software whether cessation (or reduction) influences a change in biomarker concentration and whether this increases birth weight or gestational age.

We would be remiss if we did not also consider a mediational model that includes nicotine exposure *per se* to explain increased birth weight in an NRT trial. Wisborg et al. [7] hypothesized that in their study, it was not tobacco reduction, but an independent anti-inflammatory effect of nicotine, that increased birth weight via reduced platelet aggregation. Consistent with this statement is the fact that they found no measurable effects on tobacco reduction in their study and nicotine *per se* reduces inflammation [81, 82] and platelet aggregation [83, 84]. Evidence against this argument is that nicotine levels in two NRT pregnancy trials were similar [7] or lower in the nicotine versus placebo groups. To determine the effects of nicotine *per se* during pregnancy, we will examine effects of cotinine (independent of tobacco reduction) on pregnancy outcomes and on biomarkers.

Safety: See data and safety monitoring plan for details on safety considerations. In the case of a serious adverse event due to study treatment, the medication will be stopped and the blind may be broken by contacting research pharmacy at UCONN.

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Retention: Efforts will be made to obtain follow-up information on all subjects regardless of adherence to treatment. Letters will be mailed prior to the telephone follow-up call. Home visits to collect follow-up data will be scheduled when necessary. We will obtain permission during the informed consent process to contact a significant other to obtain the participant's current telephone number should they change residences.

Incentives: These include parking validation, bus tokens, and lunch vouchers. Participants will be reimbursed \$20 per visit for childcare and travel expenses. The use of these incentives made it possible to collect data from 75% of subjects in our completed trial [1].

Drug Handling and Accountability: We will have study personnel (the same person who will dispense the medication) transport study medication from UCONN to Baystate or Hartford Hospital and place it in the locked cabinet. If for some reason the study nurse is unable to transport drug, a research assistant will pick up the drug and pharmacy and transport to Baystate to give to study nurse who will sign off that she received the medication. A signature log has been developed for drug transport and storage (see drug accountability log).

Drug Storage: Boxes of nicotine and placebo inhaler will be labeled with a study number, kept at study sites in a locked filing cabinet (with a daily temperature log) in a research room or research pharmacy at each recruitment site.

Training of counselors: Dr. Dornelas will train the nurses to deliver smoking cessation counseling using standardized procedures. One of the nurses is Spanish speaking. Counselors will be trained using videotaped case examples from prior studies [1, 58]. A treatment manual and adherence checklist that were developed by Dr. Dornelas will be adapted for this study. Nurses will be judged to be competent at behavioral counseling when they have: 1) completed two 2-hour didactic educational sessions on the theory and methods of the treatment; 2) shadowed the trainer (Dr. Dornelas) for 2 visits and 3) had the trainer sit in on 2 cases with them and judged to meet a criterion level. The trainer will remain available for the duration of the study for supervision as needed and follow up on any psychological issues or referrals that are needed. At each counseling session, the nurse will complete an adherence checklist. Counseling sessions may be audio taped and 15% may be selected at random and reviewed for adherence to the treatment protocol.

Monitoring and Auditing: Since Dr. Oncken holds the IND for this study, she is considered the sponsor and has the ethical, legal, and scientific obligation to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. Periodic monitoring visits will be scheduled as necessary at each site based on enrollment at each site. The sponsor's designee will be responsible for auditing this study. The study monitoring will be done at each site initially after the site has enrolled the first 5 subjects and then it will be done approximately every two to three months or as frequently as necessary to be determined by the investigator/monitor.

Monitoring will include:

- a. Verification that the staff and facilities, including laboratories and equipment remain adequate throughout the trial period (which will include review of staff delegation log, examining carbon monoxide calibration logs, freezer logs for specimen storage)
- b. Verification that
 - i. written informed consent was obtained before each subject's participation in the trial in accordance with 21 CFR Parts 50 and 56,

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- ii. enrolled subjects met eligibility criteria and
- iii. all study procedures are completed as outlined in the study protocol.
- c. Verification of protocol adherence and verification that all deviations from the protocol are documented with an explanation of circumstances.
- d. Verification that subjects failing to complete the study and the reason for each failure are noted
- e. Performance of a serious adverse event review; with emphasis on the proper follow-up and reporting of adverse events
- f. Verification of investigational product accountability (review drug handling, drug accountability, drug temperature logs, review each chart for physician sign off).
- g. Performance of a review of the study regulatory file
- h. Performance of a review of the data and safety monitoring plan meeting minutes/notes.

Timetable:

Expected Start Date: 12/1/10

Timeline of Study Procedures (including time to administer questionnaires and other procedures):

Assessment	Pt time (min)	Screen	Baseline (wk -1 before QD)	Visit 1 (wk 1 after QD)	Visit 2 (wk 2 after QD)	Visit 3 (wk 3 after QD)	Visit 4 (wk 4 after QD)	Visit 5 (wk 6 after QD)	Visit 6 (32-36 wk GA)	Visits 7** & 8 (1 & approx. 6 months postpartum)
Visit window				+/- 4	+/- 4	+/- 4	+/- 4	+/- 10	N/A	V.7(+/- 7), V.8(+/- 14)
Demographics	2	X								
Smoking and FTND	10	X								
Medical Screen	20	X								
Social Support and Self-Efficacy Questionnaires	5	X								
PRIME-MD PHQ	2	X	X		X			X	X	
Vital signs & Weight	5	X	X	X	X	X	X	X	X	
Nicotine Use Survey	1	X	X	X	X	X	X	X	X	x
Cotinine, Biomarkers, and hydroxycotinine/cotinine ratio	5		X		X			X	X	
Carbon monoxide	2	X	X	X	X	X	X	X	X	x
Urine sample as backup	5		X		X			X	X	
Smoking cessation counseling ^a	10		X ^a	X ^a	X	X	X	X	X	
MNWS	2		X	X	X	X	X	X		

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Adverse Effects	2		X	X	X	X	X	X	X	
Concomitant Medication	2	X	X	X	X	X	X	X	X	
Medication Dispensement	5		X		X		X			
Inhaler Usage	2			X	X	X	X	X	X	
Assignment Question	1					X				
Birth Outcomes*	30									

*Information obtained by chart review by study personnel; ** phone interview; GA = Gestational Age; QD=Quit Date; ^a Counseling will be approximately 35 minutes for the first 2 sessions, and 10 minutes for subsequent sessions; ^b Proposed medication dispensing times. If the subject misses a visit, drug may be dispensed at a subsequent visit.

Timeline of Performance Goals for the entire study:

Activity	Year 1	Year 2	Year 3	Year 4	Year 5
Staff training & preparation					
Subject enrollment					
Endpoint assessments (32-34 wk gestation)					
1- and 6-month post-partum assessments					
Data entry & cleaning					
Data analyses					
Report writing					

➤ Expected Completion Date: **February, 2017**

Budget / resources:

See attached proposed budget. The actual budget will depend on NIH funds.

Dissemination:

We intend to publish our findings in a journal article when completed, and present it at SRNT annual meeting.

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APPENDIX A
Additional Details Pertaining to Study Design for Clinical Trials

Appendix A must be completed for investigator/student initiated research projects that require review by the convened board. For example, studies that use investigational test articles, that present more than minimal risk to subjects, or that involve prisoners, must be reviewed by the convened board.

Note that for studies requiring review by the convened board the full board application must be completed, data safety monitoring must be addressed (e.g. by completion of Appendix B to the main application) and the Investigator Brochure and /or package insert must also be submitted if available.

1. *For a clinical trial (e.g. a Phase I, II or III study), the use of the intervention must be fully described e.g., the treatment regimen for use of drugs, placebo, medical device etc. Also include plans for receipt of test article, storage, dispensing and reconciliation.:*

Treatment Regimen: We will administer a 6-week course of therapy, consistent with instruction on the package insert. Subjects will receive nicotine or placebo inhaler (1:1 ratio). Pfizer Pharmaceuticals has agreed to supply us with nicotine inhaler and placebo treatments (see letter of support). To enhance compliance and to confirm patient reports and proper inhaler use, subjects will be asked to keep a daily diary of the number of cartridges used and to return all cartridges at the next study visit. Subjects will be instructed to return study medication when they receive their reminder telephone call regarding upcoming appointments. For convenience, subjects will receive a plastic container to transport study drug. Patients will be instructed on an individualized basis to taper their use over the next 6 weeks. If a study subject does not quit smoking during the first 6 weeks of active treatment, it is unlikely that she will quit during the medication taper. Consequently, at visit 5 (6 week visit), subjects who have not quit smoking (7 day point prevalence abstinence confirmed with exhaled carbon monoxide measurement) will be discontinued from medication treatment and reminded to return all study medication.

Subjects will be instructed to begin using the inhaler on their quit date. Our choice of dosage is aimed at relieving withdrawal symptoms, so we will encourage heavier smokers to use more inhaler cartridges than lighter smokers. Subjects who smoke ≥ 10 CPD will be instructed to begin with 4-12 cartridge inhalers/day, which is consistent with other inhaler studies that have recommended a minimum use of 2 inhalers per day [67], or 4 inhalers per day [66], although use of at least 6 inhalers per day was recommended by others [40], including the package insert. However, clinical efficacy is observed with use of at least 4 cartridges per day, which is the minimum dose we will recommend for women who smoke ≥ 10 CPD. Women who smoke 5-9 CPD will be instructed to begin by using 1-4 cartridge inhalers/day, based on an estimated 1-2 mg of nicotine per cigarette, with each cartridge inhaler estimated to release 4 mg of nicotine [6]. Use of 1-4 cartridges/day by 4 light smokers in the pilot study resulted in 62% nicotine replacement. Dosage adjustments will be made in response to withdrawal symptoms and cotinine levels. We will monitor cotinine levels after the women have used the inhaler for 2 weeks. Subjects will be notified by the research nurse if there is a significant increase in cotinine above baseline values while smoking (see DSMP for cotinine monitoring). In our previous study [1], this approach worked well previously to ensure that cotinine levels were not excessive.

Receipt: We will have study personnel (the same person who will dispense the medication) transport study medication from UCONN to Baystate or Hartford Hospital and place it in the locked cabinet. If for some reason the study nurse is unable to transport drug, a research staff will pick up the drug from pharmacy and transport to Baystate to give to study nurse who will sign off that she received the medication. A signature log has been developed for drug transport and receipt (see drug accountability log).

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Storage: Drug will be stored on site in locked filing cabinet. A temperature log, which can be downloaded on a weekly basis, will provide evidence that the medication is kept within recommended guidelines (not to exceed 77 degrees Fahrenheit).

Dispensing and reconciliation: The study medication will be dispensed by the research nurse at baseline, Visit 2, and Visit 4. At or before the baseline visit, the study nurse will fax key variables for a given subject to the research pharmacist at UCONN who will enter these variables into a specially developed computer algorithm. Once the pharmacist enters these variables into the computer program, the computer assigns a treatment assignment. The pharmacist will communicate with the study nurse (by fax or e-mail) which medication box # to dispense to the subject. Boxes of nicotine and placebo inhaler will be labeled with a study number, kept at study sites in a locked filing cabinet (with a daily temperature log) in a research room or research pharmacy depending on the site.

Reconciliation: At every visit, subjects are asked to return used cartridges and unused medication. Used cartridges will be validated with patient reports of study records of use. Unused medication will be sent back to pharmacy where it will be destroyed.

2. *Provide a description of known adverse events due to the intervention and the plan to deal with such adverse events (e.g. does reduction, removal of device, removal from trial.):*

A. Potential Risks:

The potential risks for subjects include blood drawing, psychological tests, breach of confidentiality, and risk of medication (adverse effects and serious adverse events and increased nicotine exposure). Medical histories will be reviewed prior to entry into the study at screening and subjects will be under medical supervision while in the study. Trained phlebotomists will draw all blood samples. Blood drawing may result in slight discomfort, bruising, or there may be soreness at the puncture site. In some instances, dizziness or fainting may occur.

It is not known which of the adverse pregnancy outcomes associated with cigarette smoking may be a result of nicotine. These adverse effects include 1) spontaneous abortion; 2) preterm delivery; 3) low birth weight; 4) preterm delivery or preterm premature rupture of membranes; 5) placenta abruption and placenta previa; 6) sudden infant death syndrome.

In phase 3 studies, the most common side effects with nicotine inhaler include cough, throat irritation, rhinitis and mouth irritation. We expect that these side effects will also occur in our population.

The physiological, subjective and behavioral measures of withdrawal, will be physically noninvasive and should present no psychological and minimal medical risk to the subject.

Although uncomfortable, withdrawal symptoms do not pose significant health risks smoking cessation results in increased irritability, anxiety, tension, depression, increased hunger and drowsiness. Some individuals may be a risk for depression with smoking cessation. This is particularly true for persons with a past history of depression.

B. Procedures to minimize risks:

- 1) **Blood draw-** sterile techniques will be utilized for blood drawing to reduce the risk of infection.
- 2) **Risk of breach of confidentiality-** All data obtained through questionnaires will be kept in a double lock system. Data collected at study visits will take the form of subjective measures (case report forms) and/or directly into the REDCap system. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data

downloads to common statistical packages; and 4) procedures for importing data from external sources. An electronic file that links patient name and number will be maintained and managed using REDCap electronic data capture tools hosted at UConn Health.

Once a subject has completed the study the informed consent form and the case report form with identifiable information (subject information/locator information) will be kept at the site of recruitment in a locked file cabinet. The rest of the case report forms that do not contain identifiable data will be sent to UConn Health. Once the study is closed in the IRB, all data will be sent to IRON mountain for long term storage until the data can be destroyed per IRB and FDA regulations.

- 3) **Psychological testing-** trained personnel will administer psychological tests.
- 4) **Medication adverse events:** a) inhaler adverse effects---To minimize potential adverse effects of the inhaler we will a) instruct subjects on proper usage; b) inform subjects to stop medication use 6 weeks after the quit date if they have not completely quit smoking. c) procedure to minimize the risk of increased nicotine exposure--- Although cotinine concentrations are not typically measured during smoking cessation trials, pregnant women are considered a vulnerable population who may be at risk for adverse effects from nicotine. Therefore we would like to ensure that subjects do not receive increased overall nicotine exposure from the nicotine inhaler than is usually obtained from smoking. As stated in the consent we recommend that subjects quit smoking completely when they start inhaler use. Serum cotinine concentrations will be collected at baseline (i.e., while smoking), and at visit 2 (approximately 1-2 weeks after inhaler use). After sample collection of serum from baseline and visit 2, these samples will be sent out for analyses to Yale University where samples will be analyzed on a weekly basis (see attached letter of support). The R.N. responsible for ongoing patient care at each site will keep a log of cotinine concentrations for each subject while smoking and while on nicotine or placebo inhaler. Subjects will be notified immediately by the R.N. if their cotinine concentrations obtained at visit 2 exceeds concentrations obtained while smoking. A serum cotinine concentration while on treatment that exceeds a subject's baseline or screening smoking levels by 40% will be considered an increase in overall nicotine exposure. Please note that this is a conservative approach because the normal individual variation of serum cotinine in pregnant women who continue to smoke is 30% (Oncken, et al 1996). If a subject is notified to decrease her inhaler use accordingly (or completely quit smoking if she is not totally abstaining from cigarettes). A repeat cotinine concentration will be repeated within a week on the new dosage regimen. If the repeat cotinine is elevated compared to baseline values as described above, the medication will be stopped. It is also noteworthy that we are examining an intermittent nicotine delivery system in this study in an attempt to minimize nicotine exposure. It would be difficult for a subject to smoke and use the inhaler at the same time, so we anticipate that nicotine exposure will not exceed baseline levels while smoking. Also, if a subject clinically significantly increases her smoking while on treatment [ie., 1) she stopped smoking at visit 2 using the inhaler, but starts smoking at a later visit and continues to use the inhaler or 2) if she increases the average number of cigarettes per day over the previous 7 days by 25% compared to visit 2], we will perform a repeat cotinine test at the visit where this is identified. A significant change in smoking patterns and/or inhaler use will be decided by the research nurse. If this cotinine test is elevated compared to baseline levels, the elevated cotinine will be handled as above. Subject's who discontinue the study early will be asked to return the inhaler, including any unused cartridges, and no inhalers will be dispensed to the subject from this point.

If for any reason we are unable to obtain blood for serum cotinine, overall nicotine exposure will be assessed with the nicalert urine test at each visit. With this system there are 5 levels of exposure (Level 0: 1-10, Level 1: 10-30, Level 2: 30-100, Level 3: 100-200, Level 4: 200-500, Level 5: 500-1000, and Level 6 1000 plus) and an increase in any

level would be consistent with an increase in exposure. This type of monitoring was utilized in one clinical trial that was monitored by the FDA to estimate overall nicotine exposure in pregnant women (33).

- 5) **Pregnancy adverse problems**---We are only including subjects with chronic stable medical problems and no imminent pregnancy problems will be enrolled into the study. If there any questions regarding current pregnancy problems the case will be discussed with the primary care provider (after obtaining consent from subject) and also reviewed with study obstetricians. We are monitoring nicotine exposure in both groups which may decrease the risk of adverse pregnancy problems. Additionally, women receive a comprehensive behavioral intervention designed to help them quit smoking, which should decrease the risk of pregnancy adverse effects. Women are monitored closely throughout the study and if an adverse event occurs consultation and treatment will be coordinated with their obstetrician.
- 6) **Withdrawal and worsening mood symptoms**--- although uncomfortable, nicotine withdrawal symptoms (irritability, craving for cigarettes, insomnia, increased appetite/weight gain, depressed mood) do not propose a significant medical risk. Nicotine replacement is designed to relieve withdrawal symptoms. Some studies suggest that especially persons with a history of depression may be at an added risk of depression with smoking cessation; however, we did not observe this in our last study (Oncken et al., 2008). If depressive symptoms occur (as evidenced by patient report or worsening symptoms on the beck questionnaire), the subject will be seen by a masters level counselor or Dr. Dornelas. Dr. Dornelas will help devise the treatment plan. Subjects who experience significant increases in depressed mood will be referred for further evaluation and treatment.

3. *Describe circumstances that may lead to a subject being removed from the trial by the PI, e.g. due to failure to follow study procedures, and the process for doing so:*

We do not foresee withdrawing any subject from the study (since it is important to have as much information as possible in an efficacy and safety study), but may withdraw study drug if a subject is noncompliant or has a serious adverse event, or if they are still smoking after 6 weeks of treatment. If a participant either withdraws from the study or the investigator decides to discontinue a participant due to SAE, the participant will have appropriate follow-up medical monitoring. Monitoring will continue until the problem requiring hospitalization was resolved or stabilized with no further change expected, is clearly unrelated to study medication, or results in death.

4. *Describe any stopping rules for the study:*

The stopping rules will be established at the first DSMB meeting, and agreed upon by both the investigative team and the DSMB. We propose to place particular emphasis was made on monitoring of overall serious adverse events, nicotine exposure, and efficacy rates. We propose that the board review serious adverse events by treatment group on an ongoing basis (approximately twice a year or more or less often depending on subject accrual). As in our previous study, a table will provided to the board with treatment groups designated as “A” and “B” in order to maintain study medication assignment blinding. The 4 types of events are (1) perinatal mortality (includes stillbirths, miscarriage after 28 weeks gestation, infant death), (2) spontaneous abortion (i.e., miscarriage prior to 28 weeks gestation), and (3) low birth weight (LBW) and (4) preterm delivery and (5) any other serious adverse events. General stopping rules proposed include 1) A significantly higher rate of subjects have low birth rates or other serious adverse events in group “A” or “B”; 2) determination that the increased incidence is related to study medication; 3) the emergence of unexpected serious adverse experience of unexpected serious adverse experience not specified in the study; 4) the board may recommend to stop the study after review of efficacy data once half the subject have been recruited if it appears to be little chance that a difference in efficacy will be observed between the 2 groups.

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As in our last study, these proposed monitoring rules were used as guidelines. Raw data, percentages, and statistics (if requested) were presented to the DSMB meetings. The DSMB has the ultimate decision as to whether the blind should be broken and the trial should remain open.

5. Additional Comments by PI:

None