

**A Pilot Randomized, Placebo-Controlled, Crossover Study of  
the Effect of the Nicotine Nasal Spray and Varenicline on  
Cigarette Smoking following Methadone Dosing in  
Methadone-Maintained Patients**

**PI: Theresa Winhusen, Ph.D.**

**Version: 4.6  
Date: February 17, 2017**

## TABLE OF CONTENTS

<b>1.0 LIST OF ABBREVIATIONS.....</b>	<b>4</b>
<b>2.0 STUDY SCHEMA.....</b>	<b>4</b>
<b>3.0 STUDY SYNOPSIS.....</b>	<b>5</b>
<b>4.0 BACKGROUND AND RATIONALE.....</b>	<b>6</b>
<b>5.0 STUDY OBJECTIVES.....</b>	<b>7</b>
5.1 PRIMARY OBJECTIVE.....	7
5.2 SECONDARY OBJECTIVES .....	7
<b>6.0 STUDY DESIGN .....</b>	<b>7</b>
6.1 OVERVIEW OF STUDY DESIGN .....	7
6.2 STUDY POPULATION .....	8
6.3 STUDY DURATION .....	8
6.4 PARTICIPANT SELECTION .....	8
6.4.1 <i>Inclusion Criteria</i> .....	8
6.4.2 <i>Exclusion Criteria</i> .....	9
6.5 OUTCOME MEASURES .....	9
6.5.1 <i>Primary Outcome Measure</i> .....	9
6.5.2 <i>Secondary Outcome Measures</i> .....	10
6.5.3 <i>Screening/Baseline Measures</i> .....	10
6.5.4 <i>Safety Measures</i> .....	11
6.5.5 <i>Other Measures</i> .....	12
6.6 RANDOMIZATION PLAN .....	12
6.7 STUDY TREATMENTS.....	13
<b>7.0 STUDY PROCEDURES.....</b>	<b>13</b>
7.1 STUDY OVERVIEW.....	13
7.2 PARTICIPANT RECRUITMENT AND CONSENT .....	13
7.3 SCREENING/BASELINE.....	15
7.4 ACTIVE TREATMENT PHASE .....	15
7.5 FOLLOW-UP .....	15
7.6 MEDICATION AND TRIAL DISCONTINUATION .....	15
7.6.1 <i>Medication Discontinuation</i> .....	15
7.6.2 <i>Stopping Guidelines</i> .....	16
7.6.3 <i>Trial Discontinuation</i> .....	16
7.7 PARTICIPANT REIMBURSEMENT .....	17
<b>8.0 STUDY MEDICATIONS .....</b>	<b>17</b>
8.1 NICOTINE NASAL SPRAY .....	17
8.2 VARENICLINE .....	17
8.3 PLACEBO .....	17
8.4 DISPENSING STUDY MEDICATION.....	17
8.5 STORAGE .....	18
8.6 RECORD OF ADMINISTRATION .....	18
8.7 USED/UNUSED SUPPLIES .....	18
8.8 SIDE EFFECTS OF NICOTINE NASAL SPRAY .....	18
8.9 SIDE EFFECTS OF VARENICLINE .....	18
8.10 CONCOMITANT MEDICATIONS .....	19
8.11 TREATMENT PLAN.....	20
<b>9.0 ANALYTICAL PLAN .....</b>	<b>21</b>
9.1 PRIMARY HYPOTHESIS .....	21
9.2 ANALYSIS PLAN .....	21

*Varenicline and nicotine nasal spray for M-M smokers – Version 4.6*

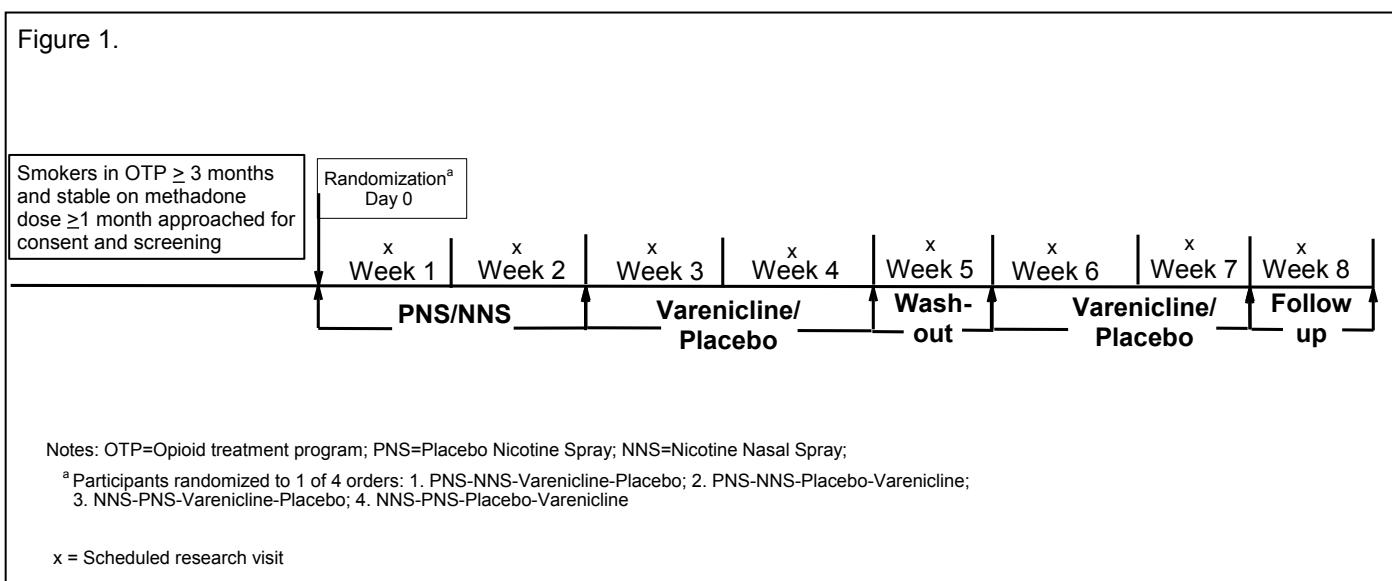
9.3 SAMPLE SIZE ESTIMATE .....	22
<b>10.0 MONITORING .....</b>	<b>23</b>
10.1 CLINICAL MONITORING.....	23
10.2 CONFIDENTIALITY .....	23
10.3 SAFETY MONITORING.....	23
10.3.1 <i>Adverse Events (AEs)</i> .....	23
10.3.2 <i>Protocol Deviation Reporting and Management</i> .....	25
<b>11.0 DATA MANAGEMENT AND PROCEDURES .....</b>	<b>26</b>
<b>12.0 REFERENCES .....</b>	<b>27</b>

## 1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CO	Carbon Monoxide
cpd	Cigarettes per day
CRF	Case report form
FTND	Fagerström Test for Nicotine Dependence
IRB	Institutional review board
M-M	Methadone-maintained
MINI	Mini International Neuropsychiatric Interview
NNS	Nicotine nasal spray
PNS	Placebo Nasal spray
PI	Principal Investigator
TLFB	Time-line follow-back
UDS	Urine drug screen
UCPC-OTP	UC Physicians Company, LLC Opioid Treatment Program

## 2.0 STUDY SCHEMA

**Figure 1: Study Schema**



### **3.0 STUDY SYNOPSIS**

**STUDY OBJECTIVES.** Smoking prevalence is over 83% in methadone-maintained (M-M) patients, these patients experience significant difficulty quitting, and there is evidence that a majority of M-M patients smoke most of their cigarettes in the 4 hours following methadone dosing. The objective is to provide a preliminary test of the ability of two pharmacological treatments, the nicotine nasal spray (NNS) and varenicline, relative to placebos, to reduce smoking during the four hours following methadone dosing.

**STUDY DESIGN.** This is a 7-week, randomized-controlled crossover study with a follow-up visit at week 8. Eligible participants will be randomized to receive the four interventions (NNS, varenicline, and placebos) in one of four orders to mitigate potential order effects.

**STUDY POPULATION.** 20 participants with elevated smoking following methadone dosing (i.e., smoking  $\geq 30\%$  of total daily cigarettes in the 4-hour post-dosing period), recruited from a large M-M program in Cincinnati Ohio, will be randomized into the study.

**TREATMENTS.** Nicotrol<sup>®</sup>NS (1 mg/dose, up to 40 doses/day), placebo for the Nicotrol<sup>®</sup>NS, varenicline tartrate (2 mg/day), and matching placebo for varenicline tartrate. Participants will be instructed not to smoke during medication evaluation weeks (weeks 1, 2, 4, and 7).

**ASSESSMENTS.** The primary outcome is the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period as assessed by the Quitbit electronic cigarette lighter. Cigarettes per day is a key secondary outcome.

**PRIMARY ANALYSIS.** The primary outcome analysis will consist of two sets of statistical analyses, one comparing the effect of NNS to PNS on the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period and one comparing the effect of varenicline to placebo on the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period.

## **4.0 BACKGROUND AND RATIONALE**

Cigarette smoking, which accounts for 443,000 deaths annually in the United States,<sup>1</sup> has an estimated prevalence of 83% in methadone-maintained (M-M) patients,<sup>2</sup> a rate four times higher than the general population,<sup>3</sup> and significantly higher than the rate observed in other outpatient substance use disorder treatment populations.<sup>2</sup> M-M patients are interested in quitting smoking<sup>4-6</sup> but experience significant difficulties with achieving smoking abstinence<sup>7-12</sup> thus more intensive smoking-cessation interventions are likely required to help M-M patients to successfully quit smoking.<sup>13</sup>

Insight into why smoking cessation is more difficult in M-M patients comes from studies evaluating the impact of opioid administration on smoking.<sup>14, 15</sup> Specifically, research has found that administration of methadone,<sup>16, 17</sup> buprenorphine,<sup>18, 19</sup> and heroin,<sup>20</sup> all increase smoking. This observed increase may be due to the ability of cigarettes to increase the rewarding properties of opioids. For example, it has been demonstrated that participants work harder to receive a methadone dose when cigarettes are available concurrently than when methadone is offered alone.<sup>21</sup> In addition, M-M patients report smoking around the time of their methadone dose to increase the pleasant effects of methadone.<sup>22</sup> Based on the observed interactions between methadone and cigarette smoking, Elkader et al. suggest that smoking-cessation treatment may need to be customized for M-M smokers, for example, by ensuring adequate nicotine replacement therapy (NRT) be available during the 2-4 hours following methadone dosing.<sup>14</sup> A study by Richter et al. also indicates that the 2-4 hours following methadone dosing is associated with greater levels of smoking, with greater rates of smoking observed in the 2 hours following dosing compared to the first 2 hours after waking,<sup>15</sup> which is the period in which the highest rate of smoking occurs in non M-M smokers.<sup>23</sup> Thus, in addition to the usual challenges faced by smokers trying to quit, M-M smokers may have an additional daily challenge following their methadone dosing. Identifying treatments that can ameliorate this challenge is of critical importance given the number of patients affected, with the number of these patients growing due to the opioid-use epidemic that has characterized recent years.<sup>24</sup>

To our knowledge, no study has evaluated the ability of smoking-cessation interventions to ameliorate increased smoking following methadone dosing in M-M smokers and, thus, there is little empirical data upon which to select interventions or to base the design of a full-scale clinical trial. The present pilot study is designed to provide important information in this regard. For example, based on data from Richter et al<sup>15</sup>, we anticipate that a majority of M-M patients (approximately 70%) will have their greatest level of smoking in the 2-4 hour post-methadone-dosing period but, to our knowledge, this finding has not yet been replicated. To be eligible for the present study, a M-M smoker must experience elevated levels of smoking in the 4 hours following methadone dosing, defined as smoking  $\geq 30\%$  of total daily cigarettes in that 4 hour time-frame. The process of screening patients for this study will provide valuable information about the relative frequency of patients who experience this level of elevated smoking during the post-methadone-dosing period. The present study will also provide preliminary information about the potential efficacy of two smoking-cessation interventions, the nicotine nasal spray (NNS) and varenicline, in reducing cigarette smoking during the four hours following methadone dosing in M-M patients.

The NNS was selected based on its ability to produce rapid peak levels of nicotine, which may approximate the rewarding effects obtained from smoking.<sup>25, 26</sup> In addition, the NNS will allow patients to individualize their dosing as needed, which might change as the effect of the methadone dose peaks. As the first study of NNS in M-M smokers, the present study will provide preliminary information about the utility of NNS in this population. One potential concern is that, in clinical trials, some patients have evidenced signs of dependence on the NNS as assessed by feelings of being dependent and by using the NNS in greater amounts or duration than recommended (package insert). The potential for developing dependence on NNS may be

## *Varenicline and nicotine nasal spray for M-M smokers – Version 4.6*

greater in M-M smokers in that they are, by definition, prone to addiction. In addition, M-M smokers have reported that methadone reduces the coughing and throat pain associated with smoking<sup>22</sup> and it may be that methadone will have a similar effect in decreasing some of the potential unpleasant effects of the NNS (e.g., sinus/eye irritation, etc. ), which could serve to increase the overall pleasant effects of the NNS.

Varenicline was selected for the present study for several reasons. As a partial agonist for the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor, varenicline should serve to decrease craving for cigarettes while also blocking their reinforcing effects and there is evidence that it is a more effective smoking-cessation treatment than bupropion.<sup>27,28</sup> A pilot trial evaluating the safety and efficacy of varenicline, relative to placebo, for cocaine-using smokers in methadone-maintenance found a decrease in the number of cigarettes per day in the varenicline group despite cocaine use being the primary focus of the study.<sup>29</sup> The present study will be the first to test the efficacy of varenicline in reducing smoking post-methadone-dosing.

## **5.0 STUDY OBJECTIVES**

### **5.1 Primary Objective**

1. To provide a preliminary test of the ability of two pharmacological treatments, the nicotine nasal spray (NNS) and varenicline, relative to placebos, to reduce cigarette smoking during the four hours following methadone dosing in M-M patients who experience elevated levels of smoking post-methadone-dosing.

### **5.2 Secondary Objectives**

1. To provide a preliminary evaluation of the ability of the NNS and varenicline, relative to placebos, to reduce total cigarettes per day in M-M patients
2. To assess the abuse liability of, and subjective feelings of dependence on, the NNS in M-M patients
3. To complete an initial evaluation of the comparative efficacy of the NNS and varenicline in reducing cigarette smoking during the 4-hours post-methadone dosing in M-M patients
4. To complete an initial evaluation of the comparative efficacy of the NNS and varenicline in reducing total daily smoking in M-M patients
5. To provide a preliminary evaluation of the ability of the NNS and varenicline, relative to placebos, to decrease opioid and nicotine withdrawal.
6. To provide a preliminary evaluation of the impact of the NNS and varenicline, relative to placebos, on the subjective experience of methadone.

## **6.0 STUDY DESIGN**

### **6.1 Overview of Study Design**

This is a 7-week, randomized-controlled crossover study with a follow-up visit at week 8. The portion of the study evaluating NNS and its placebo will be only single-blind, because of the inability to source an adequate matching placebo for the nicotine nasal spray. The portion of the study evaluating varenicline and

its matching placebo will be double-blind. Eligible participants will be randomized to receive the four interventions in one of four orders, with 5 patients assigned to each order; this design will serve to mitigate potential order effects. It should be noted that the study design is not fully counterbalanced in that varenicline and its placebo will always follow the NNS and its placebo. While it would be ideal to have a fully counterbalanced design, utilizing such a design would require an 11-week study, due to the dose escalation and washout periods required for varenicline/varenicline placebo. Given that the lack of a fully counterbalanced design impacts only the comparison of NNS and varenicline, which is a secondary objective/analysis, the decision was made to use the more efficient 7-week design.

## **6.2 Study Population**

Twenty participants, recruited from the UC Physicians Company, LLC Opioid Treatment Program (UCPC-OTP), a methadone-maintenance program in Cincinnati Ohio, will be randomized into the study. Participants will be recruited through printed and electronic advertisements at UCPC-OTP and through word-of-mouth from the UCPC-OTP staff.

## **6.3 Study Duration**

Enrollment is expected to take place over a period of approximately 6 months.

## **6.4 Participant Selection**

### **6.4.1 Inclusion Criteria**

Potential participants must:

1. be male or female, 18 years of age or older
2. be able to understand the study, and having understood, provide written informed consent in English
3. have been enrolled in the UCPC-OTP program for at least 30 days and be stable on the current methadone dose for at least 1 week
4. have smoked cigarettes for at least 3 months, have a measured exhaled CO level  $> 8$  ppm, and not planning to seek smoking-cessation treatment within the next 3 months
5. have a willingness to comply with all study procedures, including trying to stop smoking during designated weeks, and to comply with medication instructions
6. based on a week of Quitbit cigarette lighter assessments, with at least 5 days of useable data, smoke  $\geq 10$  cigarettes/day and smoke at least 30% of daily cigarettes within the 4-hour post-methadone-dosing period
7. if female and of child bearing potential, agree to use one of the following methods of birth control: oral contraceptives, contraceptive patch, barrier (diaphragm or condom), intrauterine contraceptive system, levonorgestrel implant, medroxyprogesterone acetate contraceptive injection, complete abstinence from sexual intercourse, hormonal vaginal contraceptive ring

## **6.4.2 Exclusion Criteria**

Potential participants must not:

1. have a current or past diagnosis of any psychotic disorder, or bipolar I or II disorder
2. have a psychiatric condition that, in the judgment of the study physician, would make study participation unsafe or which would make treatment compliance difficult
3. be a significant suicidal/homicidal risk
4. have a medical condition that, in the judgment of the study physician, would make study participation unsafe or which would make treatment compliance difficult. Such conditions include, but are not limited to:
  - liver function tests greater than 3X upper limit of normal
  - serum creatinine greater than 2 mg/dL
5. have had clinically significant cardiovascular or cerebrovascular disease within the past 6 months or have clinically significant ECG abnormalities
6. have taken an investigational drug within 30 days before consent
7. be taking concomitant medications that are contraindicated for use with the NNS or varenicline
8. be taking any concomitant medications that could increase the likelihood of smoking cessation (such as wellbutrin or nortriptyline)
9. have a known or suspected hypersensitivity to varenicline or the NNS
10. use/have used smoking-cessation programs with individual counseling or smoking-cessation medication treatments currently, or within 30 days before consent
11. have used electronic cigarettes or tobacco products, other than cigarettes, in the week before consent
12. be pregnant or breastfeeding
13. be anyone who, in the judgment of the investigator, would not be expected to complete the study protocol (e.g., due to relocation from the clinic area, probable incarceration, etc.)

## **6.5 Outcome Measures**

### **6.5.1 Primary Outcome Measure**

The primary outcome measure is the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period as assessed by the Quitbit electronic cigarette lighter (manufactured by Quitbit, Inc.; Providence, RI). The Quitbit lighter records the time and date each time the lighter is activated, presumably to smoke a cigarette. The data from the lighter will be extracted at each weekly research visit.

The present trial will follow a procedure analogous to that utilized by Richter et al.; the Quitbit lighter will be used solely for tracking smoking, with the smoking-reduction component of the software disengaged. Study participants will be instructed on the proper use of the lighter, including only using the lighter to light a cigarette that they are going to smoke. They will also be provided with weekly log sheets to record any equipment problems or discrepancies between the smoking events recorded by Quitbit and the “actual” cigarettes smoked by the participant.

### **6.5.2 Secondary Outcome Measures**

1. Cigarettes per day (CPD). The total number of cigarettes smoked each day will be assessed by the Quitbit lighter (see above). In addition, the Timeline Follow-back (TLFB) procedure<sup>30</sup> will be used to assess the participants’ self-reported use of cigarettes, other tobacco products, alcohol and illicit substances for each day of the study. The CPD based on the TLFB will be used in statistical analyses in the event of Quitbit lighter problems for a given day.
2. Carbon monoxide (CO) level. CO in each participant’s breath will be tested using the Bedfont Micro<sup>+</sup> Smokerlyzer<sup>®</sup> as outlined in Table 2. A CO level of  $\leq 8\text{ppm}$  will be used to verify reports of no smoking.
3. Nicotine withdrawal will be assessed with the Minnesota Nicotine Withdrawal Scale (MNWS),<sup>31</sup> a self-assessment of the intensity (i.e., 0=none at all to 4=severe) with which the respondent is experiencing 8 nicotine withdrawal symptoms.
4. Opioid withdrawal will be assessed with the Subjective Opiate Withdrawal Scale (SOWS), a self-assessment of the intensity (i.e., 0=not at all to 4=extremely) with which the respondent is experiencing 16 opioid withdrawal symptoms.<sup>32</sup>
5. Drug Effect Questionnaire (DEQ) - Subjective experience of methadone will be assessed with the 5-item DEQ, a PhenX Toolkit-recommended measure,<sup>33</sup> in which participants rate the degree to which they experience 5 drug-related effects (i.e., feel a drug effect, high, like the drug, dislike the effect, would like more drug) by making a mark along a 100-mm line from 0 (not at all) to 100 (extremely).

### **6.5.3 Screening/Baseline Measures**

1. Smoking History Survey. The Smoking History Survey is a modified version of the Mayo Nicotine Dependence Center Patient Questionnaire. It asks participants how many CPD they smoke, at what age they started smoking, number of years smoking, how many times they have attempted to quit (including methods), when the last quit attempt occurred, their longest period of cigarette abstinence, and if there are other smokers in their household. Information on other non-cigarette tobacco products will also be noted.
2. The Fagerström Test for Nicotine Dependence (FTND) is a brief self-administered assessment of cigarette use patterns that yields a single overall dependence score.<sup>34</sup>
3. Mini International Neuropsychiatric Interview, version 6.0 (MINI) will be administered by a trained interviewer to evaluate for the presence of exclusionary psychiatric disorders.
4. Blood Chemistries. During screening/baseline, blood will be collected in serum separation evacuated venous blood collection tubes. Quantitative analysis will be performed, which will include the following

analytes: glucose, creatinine, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), gamma glutamyltranspeptidase (GGT), and blood urea nitrogen (BUN). A prescription topical numbing cream may be offered to all participants prior to the blood draw.

5. Complete blood count (CBC). A CBC with differentials and platelet count will be performed during screening/baseline (from same blood draw as blood chemistries, above). Quantitative analyses for hemoglobin, hematocrit, red blood cells, platelets, total white blood cells, and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils will be performed.
6. Pregnancy Test and Birth Control Assessment. A urine pregnancy test designed to measure human chorionic gonadotropin hormone will be completed during screening. All female participants will be tested except women who have a documented hysterectomy. During screening/baseline, female participants' use of birth control and breastfeeding status will be assessed.
7. Urine drug screen (UDS). A rapid UDS system that screens for cocaine, methamphetamine, amphetamine, opioids, benzodiazepines, and marijuana will be used to analyze a screening/baseline urine sample. To avoid falsification, urine samples will be collected using temperature monitoring and the validity of urine samples will be checked with the use of a commercially available adulterant test.
8. ECG. Twelve-lead electrocardiograms will be performed during screening/baseline according to standard procedures. Ventricular rate (bpm), PR (ms), QRS (ms) and QTc (ms) will be reported on the ECG readouts. The results will be reviewed by a study physician for interpretation and for a clinical judgment about whether the participant is eligible for the study based on the ECG results.
9. Medical History. A medical history will be performed by a qualified medical staff member.
10. Physical Exam. Performance of a physical exam during screening/baseline will be done by a medical staff member qualified to perform physical exams.
11. Weight/Height. The participant's weight and height will be recorded during screening/baseline.
12. The Suicide Behaviors Questionnaire-Revised (SBQ-R) is a validated measure of suicidal behavior<sup>35</sup> that will be completed by the participant during screening/baseline. A score  $\geq 8$  will trigger a suicidal risk assessment by a qualified mental health professional.
8. 13. Methadone Maintenance Treatment Status. Only patients who have been enrolled in the UCPC-OTP program for at least 30 days and stable on the current methadone dose for at least 1 week are eligible to participate (see section 6.4.1); clinic records will be used to verify this criterion.

#### **6.5.4 Safety Measures**

1. Vital Signs. Vital signs, including blood pressure and heart rate, will be assessed according to the schedule in Table 2. Systolic blood pressures greater than 160 or less than 90 and diastolic greater than 100 and less than 60 will be brought to the attention of a study physician for review.
2. Adverse Events (AEs). AEs will be assessed by study staff as outlined in Table 2. If an AE requires medical attention, it will be reported to a study physician immediately.

3. Prior/Concomitant Medications. All medications taken by the participant for the 30 days prior to screening/baseline, during screening/baseline, and during the active study will be documented on a Prior/Concomitant Medications assessment (see Table 2).

4. Abuse liability and subjective feeling of dependence associated with the NNS/PNS will be assessed using measures that were utilized in a study of the abuse liability of, and dependence on, the nicotine patch, gum, spray, and inhaler.<sup>36</sup> Specifically, abuse liability will be assessed based on participant rating of the pleasantness/ unpleasantness and satisfaction of NNS/PNS compared with their usual cigarettes on a 9-point scale (1=very unpleasant/unsatisfying, 5=neutral, 9=very pleasant/satisfying). Subjective feeling of dependence will be assessed by participant rating of how dependent they feel on the NNS/PNS (1=definitely not, 2=possibly, 3=probably, and 4=definitely).

5. The Columbia Suicide-Severity Rating Scale (C-SSRS) is a validated assessment of suicidal ideation/ behavior<sup>37</sup>; it will be completed following the schedule outlined in Table 2. An answer of yes to items 4 or 5 (suicidal intent or plan) will trigger a suicidal risk assessment by a qualified mental health professional.

## **6.5.5 Other Measures**

### **1. Demographics**

This assessment will include questions about the participant's ethnicity, age, and sex.

### **2. Medication adherence**

Adherence with using the NNS/PNS and varenicline/placebo as prescribed will be assessed with self-report. The participants will be provided with a log for tracking their use of the nicotine nasal spray. In addition, during study weeks 3, 4, 6, and 7, when participants are scheduled to take varenicline/placebo, they will be asked to bring their bottles to the methadone dosing window so that the first dose of the day can be observed. Finally, adherence with varenicline/placebo will be assessed with pill count. Participants will be provided with information packets for Nicotrol®NS and varenicline.

## **6.6 Randomization Plan**

Eligible participants will be randomized to receive the four interventions in one of four orders as outlined in Table 1, with 5 patients assigned to each order; this design will serve to mitigate potential order effects.

**Table 1. The four medication orders to which participants will be randomized**

	<b>Week 1</b>	<b>Week 2</b>	<b>Week 3-4</b>	<b>Week 6-7</b>
<b>Order 1</b>	PNS	NNS	Varenicline	Placebo
<b>Order 2</b>	PNS	NNS	Placebo	Varenicline
<b>Order 3</b>	NNS	PNS	Varenicline	Placebo
<b>Order 4</b>	NNS	PNS	Placebo	Varenicline

Note: PNS=Placebo Nasal Spray; NNS=Nicotine Nasal Spray

Allocation sequence generation: The list of treatment assignments will be randomly generated prior to study initiation, employing a permuted-block scheme to ensure an approximately equal number of participants in each treatment group at any time during recruitment. Random assignments will be generated using standard randomization procedures in SAS software, and the master list of assignments will be stored by a non-study

staff member, in a secure, locked location. The master list will be used to assemble treatment kits prior to study initiation.

Treatment assignment: When an eligible participant is ready to be randomized, the staff member will assign the participant the next available kit (e.g., the first randomized participant gets kit #01, the second randomized participant gets kit #02, etc.). The randomizing staff member will write the assigned kit number on the participant's randomization source document, and track all treatment assignments in a master log kept with the treatment kits.

## **6.7 Study Treatments**

As described in section 8.0, all participants will receive the four study medications: NNS, varenicline, and placebos. All participants will receive their methadone dose and counseling as typically provided by the opioid treatment program (OTP). For in-clinic doses, the timing of the methadone dose will be taken from the clinic record. For take home doses, participants will be instructed to call a secure study phone when they take their methadone dose to capture the time of the dose.

## **7.0 STUDY PROCEDURES**

### **7.1 Study Overview**

Table 2 provides an overview of the participant procedures and assessments.

### **7.2 Participant Recruitment and Consent**

Interested M-M patients who have been determined by telephone or face-to-face interview to smoke 10 or more CPD, report that they smoke the most in the 4 hour period following methadone dosing, and are likely to meet other eligibility criteria are invited to receive an explanation of the study purpose and requirements. If still interested after receiving a face-to-face explanation of the study, the candidate is given an opportunity to review, inquire about, and sign the informed consent form.

Any participant who has difficulty understanding the information contained in the consent form is asked to review the misunderstood portion(s) of the consent and discuss them with a research staff member until he or she shows complete understanding of the information and may thus give full consent. Research staff members work closely with the study candidates in an effort to help them understand the requirements of their participation. Persons with literacy problems are assisted to the extent possible. Any participant who is unable to demonstrate understanding of the information contained in the informed consent is excluded from study participation.

**Table 2 Overview of study assessments and procedures**

Assessment/ Procedure	Sern/ Base	Rand	Study Weeks							FU
			0	1	2	3	4	5	6	
NNS/PNS dispensed		X	X							
NNS/PNS taken			7X	7X						
Varenicline/Placebo dispensed				X	X		X	X		
Varenicline/Placebo taken					7X	7X		7X	7X	
Medication Adherence			X	X	X	X	X	X	X	X
<b>Screening/Baseline</b>										
Informed Consent	X									
Smoking History Survey	X									
Fagerström (FTND)	X									
MINI	X									
Blood chemistry	X									
CBC	X									
Birth Control Assessment	X									
Urine Pregnancy Test	X									
Urine for UDS	X									
Electrocardiogram	X									
Medical History	X									
Physical Exam	X									
Weight/Height	X									
Substance Abuse Tx Status	X									
SBQ-R	X									
<b>Efficacy Assessments</b>										
Quitbit cigarette lighter	7X	X	7X	7X	7X	7X	7X	7X	7X	
TLFB	X		X	X	X	X	X	X	X	X
SOWS	X		X	X	X	X	X	X	X	
Drug Effect Questionnaire	X		X	X	X	X	X	X	X	
MNWS	X		X	X	X	X	X	X	X	
CO level	X		X	X	X	X	X	X	X	X
<b>Safety Assessments</b>										
Vital Signs	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Prior/Concom Meds	X	X	X	X	X	X	X	X	X	X
Abuse liability			X	X						
Subjective dependence				X	X					
C-SSRS		X	X	X	X	X	X	X	X	X

Notes: “7X” represents a procedure or assessment performed each day of the week.

### **7.3 Screening/Baseline**

After signing the informed consent form, the study participant proceeds through the screening/baseline phase. Ideally, the screening/baseline procedures will be completed in two visits, but they can be completed in fewer visits or more visits if necessary. Under certain circumstances a participant will be allowed to re-consent and repeat the screening/baseline procedures. Participants who meet study eligibility and complete screening/baseline as outlined above will be randomly assigned to one of four medication orders.

### **7.4 Active Treatment Phase**

As outlined in Figure 1, the active treatment phase is 7 weeks in duration. During this time, participants will receive all four medications and will be scheduled for one research visit per week. Participants will be instructed not to smoke during medication evaluation weeks, which are study weeks 1, 2, 4 and 7. During medication evaluation weeks (i.e., Weeks 1, 2, 4, and 7) the research visits will be scheduled to occur during day 6 or 7 of the week in order to maximize participant exposure to the medication/placebo prior to assessment. All assessments ideally will be completed after the participant has received his/her methadone dose and before the participant smokes a cigarette, with the exception of the baseline visit when participants will be allowed to smoke prior to completing the assessments.

### **7.5 Follow-up**

A follow-up visit will be completed during study week 8. The measures to be collected during this visit are delineated in Table 2.

### **7.6 Medication and Trial Discontinuation**

#### **7.6.1 Medication Discontinuation**

An investigator may discontinue a participant's medication if he or she deems it clinically appropriate or, at the discretion of the investigator, for any of the reasons listed below.

1. significant side effects that are likely to have been caused by the study medication
2. serious or unexpected AEs which would make further study medication dosing not in the participant's best interest
3. inability or unwillingness of the participant to comply with the study protocol
4. serious intercurrent illness

A participant may discontinue medication anytime s/he wishes. Participants who wish to discontinue from study medication early or to withdraw from the study will have their medication discontinued. Any participant who discontinues the study prematurely, regardless of the reason, will be requested to return for a study close-out visit at the first opportunity. Whenever a study participant stops coming to the clinic without notification, staff will make a concerted effort to contact the participant (or the designated contact person if the participant cannot be contacted) to assure that they have had no untoward effects from study participation.

Study participants withdrawn from the protocol secondary to a medical or psychiatric concern will be referred for appropriate treatment. Participants will be asked to sign a general consent for the release of information to the referred health care provider. Study staff may request transportation for emergency treatment of a participant if medically appropriate (e.g., for acutely psychotic or suicidal participants).

### **7.6.2 Stopping Guidelines**

1. Dosing must be stopped immediately if the study clinician believes that continued dosing of study medication will be detrimental to the participant's mental or physical health.
2. Dosing must be stopped immediately if a participant makes a suicide attempt anytime during study participation.
3. Dosing must be stopped immediately if a study participant becomes pregnant during study participation. The participant will be referred to medical care for the pregnancy.
4. A participant must have a risk assessment performed by a qualified mental health professional to determine whether it is safe to continue dosing if, on the C-SSRS, he or she endorses thoughts or plans to commit suicide, and also endorses some intent to act on such thoughts or plans.
5. The study participant should seek immediate medical care in the following situations and then consult the study clinician to determine if it is safe to continue dosing:
  - If he or she experiences agitation, hostility, depressed mood, or other abnormal changes in thinking or behavior;
  - If he or she develops suicidal ideation or exhibits any suicidal behavior;
  - If he or she experiences new or worsening cardiovascular symptoms;
  - If he or she has signs and symptoms of a myocardial infarction;
  - If he or she has signs and symptoms of a stroke;
  - If he or she develops a serious skin rash with mucosal lesions;
  - If he or she develops hives or angioedema;
  - If he or she experiences any other severe hypersensitivity syndrome.

Participants who stop dosing for any reason will be eligible to continue attending study visits if they choose to remain in the study. If the participant wishes to end study participation, a study close-out visit will be conducted at the first opportunity.

### **7.6.3 Trial Discontinuation**

The study sponsor has the right to discontinue the investigation at any time.

## **7.7 Participant Reimbursement**

Participants will be reimbursed for their transportation, inconvenience, and time. This reimbursement will be in the form of gift cards or a Greenphire prepaid debit card. It is recommended that participants receive a total of \$70 for completing screening/baseline. To encourage participants to return the Quit Bit to the study team, a \$30 incentive payment is included at the Week 8 Follow-up Visit. The reimbursement schedule for study visits is outlined in Table 3. Using the reimbursement schedule, a participant could be reimbursed a maximum of \$365.

**Table 3: Reimbursement schedule for research visits**

Visit	Total per Visit (\$)	Total # of Visits	Grand Totals (\$)
Screening/baseline			70
Randomization Day	30	1	30
Weekly study visits (1 and 5)	35	2	70
Weekly study visits (2-4; 6-7)	25	5	125
Week 8 Follow-up visit	40	1	40
Incentive for return of the Quit Bit (Week 8)	30	1	30
Total			\$365

## **8.0 STUDY MEDICATIONS**

### **8.1 Nicotine Nasal Spray**

Nicotrol®NS (Distributed by Pharmacia & Upjohn Co Division of Pfizer Inc, NY, NY 10017) will be utilized in the study.

### **8.2 Varenicline**

Varenicline tartrate (Distributed by Pfizer Labs Division of Pfizer Inc, NY, NY 10017) will be utilized in the study.

### **8.3 Placebo**

Placebos for the Nicotrol®NS and varenicline tartrate will be obtained in cooperation with Pfizer Inc.

### **8.4 Dispensing Study Medication**

Dispensing will be completed by qualified study staff. NNS or placebo will be dispensed to participants at randomization (time "0" in Table 2) so that the use of NNS/PNS can start upon waking on the first day of study week 1. NNS/PNS or varenicline/placebo will be dispensed at weekly clinic visits as outlined in Table 2.

## **8.5 Storage**

Study medication will be stored in compliance with state law and institutional policy and in conditions as indicated on the product label.

## **8.6 Record of Administration**

Drug-accountability records including perpetual inventory, will be maintained at all times.

## **8.7 Used/Unused Supplies**

Unused study medication will be returned to the pharmacy (or other appropriately qualified entity based on local/state regulations) and logged into a perpetual inventory of study drug returned. The study staff will accurately maintain study drug accountability records.

## **8.8 Side Effects of Nicotine Nasal Spray**

The most common side effects:

- nasal irritation
- nasal congestion, rhinorrhea and sneezing
- eye irritation, watery eyes
- throat irritation, coughing
- transient changes in sense of smell or taste
- facial flushing

➤ These side effects are most common during the first week of use and generally improve with continued use of the nicotine nasal spray.

➤ The spray can be an irritant if it comes in direct contact with any mucous membrane or skin surface.

Dependence potential:

- In clinical trials, feelings of dependency on the spray were reported by 32% of active spray users compared with 13% of placebo spray users.
- Following the recommended dosing guidelines should minimize the tendency to become dependent on nicotine nasal spray.
  - The dosing guidelines recommend no more than 5 doses/hour and no more than 40 doses/24 hours.
  - Nicotine nasal spray should not be used for longer than 6 months.

## **8.9 Side Effects of Varenicline**

For patients taking the recommended dose of varenicline:

The most common side effects:

<ul style="list-style-type: none"><li>• nausea</li><li>• insomnia</li><li>• abnormal or vivid dreams</li><li>• constipation</li><li>• flatulence</li></ul>	<ul style="list-style-type: none"><li>• vomiting</li><li>• headache</li><li>• dry mouth</li><li>• general malaise or fatigue</li></ul>
--	--

Uncommon or rare, but potentially serious side effects:

<p>➤ <b>Neuropsychiatric Symptoms</b></p> <ul style="list-style-type: none"><li>• changes in mood (depression, mania)</li><li>• psychosis</li><li>• hallucinations</li><li>• paranoia</li><li>• delusions</li><li>• homicidal ideation</li><li>• hostility</li><li>• agitation</li><li>• anxiety</li><li>• panic</li><li>• worsening of pre-existing psychiatric illness</li><li>• suicidal ideation</li><li>• suicide attempt</li><li>• completed suicide</li></ul> <p>➤ <b>Skin reactions</b></p> <ul style="list-style-type: none"><li>• Stevens-Johnson Syndrome</li><li>• Erythema multiforme</li></ul>	<p>➤ <b>Cardiovascular Events</b></p> <ul style="list-style-type: none"><li>• Angina pectoris</li><li>• Nonfatal myocardial infarction</li><li>• Need for coronary revascularization procedure</li><li>• New diagnosis of peripheral vascular disease</li><li>• Need for procedure to treat peripheral vascular disease</li></ul> <p>➤ <b>Hypersensitivity Reactions</b></p> <ul style="list-style-type: none"><li>• swelling of the face, mouth (tongue, lips, and gums)</li><li>• swelling of extremities</li><li>• swelling of the neck (throat and larynx)</li><li>• angioedema</li></ul>
--	---

## 8.10 Concomitant Medications

Any medication (including prescription, over-the-counter, herbal supplements and health store products) to be taken during the study ideally should be approved by a study physician.

### Excluded Medications:

*These should not be taken for 30 days prior to study randomization and should not be used or prescribed for use during study participation:*

- Anticonvulsants
- Antiretroviral medications
- Biologics including human monoclonal antibody drugs such as HUMIRA
- Bupropion
- Insulin
- Naltrexone
- Nortriptyline
- Theophylline
- Warfarin
- Stimulants and appetite suppressants, either prescribed or over-the-counter, including Kava Kava and St. John's Wort
- Electroconvulsive therapy (ECT)
- Nicotine replacement therapy and other aids to smoking cessation which are not dispensed as study medication

### Episodic Use Permitted

*Please discuss with study physician if these are used within 30 days prior to screening visit:*

- Oral and injectable steroids are permitted on a short-term basis only

### **Chronic Use Permitted**

*These can be used without restrictions:*

- Acetaminophen
- Antidepressant medications, other than bupropion or nortriptyline
- Antihistamines
- Antihypertensive agents
- Aspirin
- Benzodiazepines (non-benzodiazepine hypnotics are also allowed)
- Bronchodilators
- COX-2 selective and non-selective medications, including NSAIDs
- Hormone Replacement Therapy
- Inhaled steroids
- Lipid-lowering agents
- Multivitamins
- Oral and depot contraceptives
- Oral diabetes medications
- Thyroid replacement
- Concomitant psychotherapy, phototherapy or light therapies

### **8.11 Treatment Plan**

Table 4 delineates the dosing schedule and the weeks during which medication efficacy will be evaluated. All participants will use NNS/PNS during days 1-7 of study weeks 1 and 2 and will be instructed to utilize the spray and to not smoke during those weeks. Participants will be taught how to deliver a 0.5 mg spray in each nostril and will be instructed that they may use the spray up to 40 times a day but no more than 5 times an hour. Participants will undergo dose escalation of varenicline/placebo during study weeks 3 and 6, and will be on full dose during weeks 4 and 7. Participants who are unable to tolerate the target dose (2 mg/day) will be titrated to the highest dose tolerated. Participants will be instructed to not smoke during weeks 4 and 7, which are the weeks during which the efficacy of varenicline/placebo will be assessed. It should be noted that participants assigned to a medication order in which varenicline is given before varenicline placebo (i.e., orders 1 and 3 in Table 1), will have a two-week washout period before placebo is tested - the first week is the official "wash out" week during week 5 and the second is week 6 during which the participant is undergoing dose escalation for placebo.

**Table 4: Schedule of medication dosing and evaluation of medication effect**

<b>Week</b>	<b>Day</b>	<b>Medication/Placebo</b>	<b>Dose</b>	<b>Evaluation of Medication Effect</b>
<b>1</b>	1-7	NNS/PNS	1 mg/dose up to 40x/day	Week 1
<b>2</b>	1-7	NNS/PNS	1 mg/dose up to 40x/day	Week 2
<b>3</b>	1-3	Varenicline/Placebo Dose Escalation	0.5 mg once daily	
	4-7		0.5 mg twice daily	
<b>4</b>	1-7	Varenicline/Placebo	1 mg twice daily	Week 4

5		Wash out		
6	1-3	Varenicline/Placebo	0.5 mg once daily	
	4-7	Dose Escalation	0.5 mg twice daily	
7	1-7	Varenicline/Placebo	1 mg twice daily	Week 7

Note: PNS=Placebo Nasal Spray; NNS=Nicotine Nasal Spray

## 9.0 ANALYTICAL PLAN

### 9.1 Primary Hypothesis

This study will test the hypothesis that, in M-M patients who experience elevated smoking during the 4-hour post-methadone-dosing period, both NNS and varenicline, relative to placebos, will reduce smoking during the post-methadone-dosing period.

### 9.2 Analysis Plan

All analyses will be completed using SAS, Version 9.3 (SAS Institute, 2010).

1. Primary outcome analysis. The primary outcome analysis will consist of two sets of statistical analyses, one comparing the effect of NNS to PNS on the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period and one comparing the effect of varenicline to placebo on the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period. The statistical approach taken to both sets of analyses will be the same. A normal mixed model regression will include treatment (active vs. placebo) and the proportion of cigarettes smoked during the post-methadone-dosing period during baseline as covariates. In addition, corrected Akaike Information Criterion (AICC), will be used to determine whether treatment order (see Table 1), time (days 1-7), and / or the treatment-by-time interaction should be included as covariates in the mixed model regression. The dependent variable will be the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period from the weeks during which the medication/placebo is being evaluated (see Table 2). The baseline urine drug screen result (positive or negative for substances other than opioids) will be controlled for in the analyses.

2. Secondary outcome analyses. The present trial has six secondary objectives, the analytic approach taken for each is described below. The baseline urine drug screen result (positive or negative for substances other than opioids) will be controlled for in the analyses.

2a. Preliminary evaluation of the ability of the NNS and varenicline, relative to placebos, to reduce total cigarettes per day (CPD). This secondary outcome analysis will consist of two sets of statistical analyses, one comparing the effect of NNS to PNS on CPD and one comparing the effect of varenicline to placebo on CPD. The analytic approach utilized for the primary outcome analysis will be used for this analysis with the variable of interest being CPD (i.e., as opposed to the proportion of daily cigarettes smoked during the post-methadone-dosing period).

2b. Assessing the abuse liability of, and subjective feelings of dependence on, the NNS. The effect of NNS, compared to PNS, on the liability scale will be assessed using the same analysis procedure used for the primary outcome. The effect of treatment on the four-point dependence measure will be assessed with the same analysis procedure except that instead of a normal mixed model regression, a proportional odds logistic mixed model regression will be used.

2c. Exploratory analysis of the comparative efficacy of the NNS and varenicline in reducing cigarette smoking during the 4-hours post-methadone dosing period. The effect of NNS, compared to varenicline, on the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period will be assessed using the same analysis procedure used for the primary outcome except that instead of comparing each experimental treatment to its respective placebo, the experimental treatments will be compared to each other. Because the order of NNS and varenicline is not counterbalanced (i.e., NNS is always received prior to varenicline), any significant differences may be due to an order effect and, thus, this is considered an exploratory analysis only.

2d. Exploratory analysis of the comparative efficacy of the NNS and varenicline in reducing total daily smoking in M-M patients. The analytic approach described in 2c will be used for this analysis with the variable of interest being CPD.

2e. Preliminary evaluation of the ability of the NNS and varenicline, relative to placebos, to decrease opioid and nicotine withdrawal. The analytic approach utilized for the primary outcome analysis will be used for these analyses with the variables of interest being SOWS total score and MNWS total score.

2f. Preliminary evaluation of the impact of the NNS and varenicline, relative to placebos, on the subjective experience of methadone. The analytic approach utilized for the primary outcome analysis will be used for these analyses with the variables of interest being each of the 5 items on the DEQ.

### **9.3 Sample Size Estimate**

The power analysis was completed for the primary outcome measure, which is the proportion of daily cigarettes smoked during the 4-hour post-methadone-dosing period. The power calculation was based on data from Richter et al. who evaluated the proportion of daily cigarettes smoked in the 2 - 4 hours post-methadone-dosing. These investigators reported a standard deviation of .135 for the proportion of daily cigarettes smoked during the 2 hour post-methadone-dosing period.<sup>15</sup> The present trial will be evaluating a 4 hour period and, to be conservative, we assumed a standard deviation of .27 for the power analysis.

Assuming a two-sided test, an alpha of .05, and a within-subject correlation of .80, a sample size of 20 will provide 78% power to detect a mean difference of .11, which corresponds to a Cohen's d of .41, as statistically significant. In the present study, eligible participants will, during baseline, use at least .30 of their daily cigarettes during the 4-hour post-methadone-dosing period; for a participant using .30 during baseline, a reduction to .19 or lower would be in the range of a statistically-significant change. Based on the eligibility criteria and the fact that we are utilizing M-M patients, who have a very high rate of retention, we are assuming that all 20 randomized participants will complete the study. If only 18 of the participants complete the study, using the assumptions outlined above, we would have 78% power to detect a mean difference of .12, which corresponds to a Cohen's d of .43, as statistically significant.

## **10.0 Monitoring**

### **10.1 Clinical Monitoring**

Qualified personnel will ensure study procedures are conducted and that study data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulations.

Study documentation includes all case report forms, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

### **10.2 Confidentiality**

Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

### **10.3 Safety Monitoring**

#### **10.3.1 Adverse Events (AEs)**

The Investigator may appoint a Study Clinician for this study, who will review or provide consultation for each Serious Adverse Event (SAE) as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. The study staff will be trained to monitor for and report adverse events and Serious Adverse Events.

#### **Definitions of Adverse Event and Serious Adverse Event**

**Adverse Event:** An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. (Any change from baseline in clinical status, ECGs, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator are considered AEs.)

**Suspected adverse reaction** is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

**Adverse reaction** is any adverse event caused by the study drug/intervention.

**Serious Adverse Event (SAE):** A serious adverse event (SAE) refers to all serious events including serious adverse events or serious suspected adverse reaction or serious adverse reaction as determined by the study investigator or the sponsor is any event that results in any of the following outcomes:

1. Death: A death occurring during the study or which comes to the attention of the investigator during the protocol-defined follow-up after the completion of the study, whether or not considered treatment-related, must be reported.
2. Life-threatening AE (Life-threatening means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.)
3. Inpatient hospitalization or prolongation of existing hospitalization
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital abnormality or birth defect
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

**Unexpected Adverse Event:** Any adverse event, the specificity or severity of which is not consistent with the investigator brochure or the package insert. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

**Pregnancy:** Any pregnancies that occur on study will be captured on a pregnancy CRF and not separately reported as an AE or a serious event. Women who become pregnant during the study period will be discontinued from further study drug/intervention and referred for medical care.

**Medical History:** A thorough medical history during the eligibility assessment phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

**Eliciting and Reporting Adverse Events:** Appropriately qualified and trained research personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Research personnel will obtain as much information as possible about the reportable AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Reporting of serious events to the IRB will occur per the IRB's guidelines.

Additional information may need to be gathered to evaluate the SAE and to complete the appropriate CRFs. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stabilized at the time of initial reporting or if new information becomes available, follow-up information must be submitted as soon as possible.

Reportable AEs/SAEs will be followed until resolution or stabilization or study end, and any serious and study-related AEs will be followed until resolution or stabilization even beyond the end of the study.

### **Reportable Serious Adverse Events**

For the present study, the following SAEs will not be recorded in the data system nor reported to IRB.

- Admission to a hospital/surgery center for preplanned/elective surgeries;
- Admission to a hospital for scheduled labor and delivery

### **Assessment of Severity and Causality**

The study medical clinician will review reportable AEs and SAEs for seriousness, severity, and causality on at least a weekly basis.

Guideline for Assessing Severity: The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (< 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guideline for Determining Causality:

The study investigator will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

**Participant Withdrawal:** The investigator in consensus with a study physician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be discontinued from study drug/intervention. If necessary, the investigator may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant should be asked to complete an end of study visit assessment and be referred to appropriate medical care and followed until the symptoms of any adverse event resolve or their condition becomes stable.

### **10.3.2 Protocol Deviation Reporting and Management**

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, significant versus non-significant. Significant deviations include those that significantly affect the safety of the participant, the safety of the researchers, or the scientific quality of

the study. Non-significant deviations are those that are highly unlikely to impact safety of the participants or scientific integrity of the study. All protocol deviations will be noted and reported to the IRB as required.

## **11.0 DATA MANAGEMENT AND PROCEDURES**

### **11.1 Data Acquisition and Transmission**

All research staff will be trained in Good Clinical Practice (GCP) guidelines. All diagnostic, efficacy and tolerability data collected will be in the form of diagnostic and rating instruments, electronic record from the Quitbit cigarette lighter, and results from laboratory tests. All information collected will be de-identified. Only research staff members that are directly involved with patient care and study procedures will have access to patient identity.

### **11.2 Data Entry and Management**

Most data collected for the current study will be captured first on paper CRFs that will match closely the electronic data entry forms designed to facilitate entry of those data into the database. Entry into the database will be performed by the study research assistants and other study staff members who have been trained to perform this task. After database lock, data will be downloaded to the statistical package being used for data analysis.

## 12.0 REFERENCES

1. Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses--United States, 2000-2004. *MMWR Morb Mortal Wkly Rep.* Nov 14 2008;57(45):1226-1228.
2. Guydish J, Passalacqua E, Tajima B, Chan M, Chun J, Bostrom A. Smoking Prevalence in Addiction Treatment: A Review. *Nicotine & Tobacco Research.* Jun 2011;13(6):401-411.
3. Schroeder SA. A 51-Year-Old Woman With Bipolar Disorder Who Wants to Quit Smoking. *Journal of the American Medical Association.* Feb 4 2009;301(5):522-531.
4. Clemmey P, Brooner R, Chutuape MA, Kidorf M, Stitzer M. Smoking habits and attitudes in a methadone maintenance treatment population. *Drug and Alcohol Dependence.* Mar 14 1997;44(2-3):123-132.
5. Richter KP, Gibson CA, Ahluwalia JS, Schmelzle KH. Tobacco use and quit attempts among methadone maintenance clients. *American Journal of Public Health.* Feb 2001;91(2):296-299.
6. Frosch DL, Shoptaw S, Jarvik ME, Rawson RA, Ling W. Interest in smoking cessation among methadone maintained outpatients. *Journal of Addictive Diseases.* 1998;17(2):9-19.
7. Richter KP, McCool RM, Catley D, Hall M, Ahluwalia JS. Dual pharmacotherapy and motivational interviewing for tobacco dependence among drug treatment patients. *Journal of Addictive Diseases.* 2005;24(4):79-90.
8. Reid MS, Fallon B, Sonne S, et al. Smoking cessation treatment in community-based substance abuse rehabilitation programs. *Journal of Substance Abuse Treatment.* Jul 2008;35(1):68-77.
9. Shoptaw S, Jarvik ME, Ling W, Rawson RA. Contingency management for tobacco smoking in methadone-maintained opiate addicts. *Addictive Behaviors.* May-Jun 1996;21(3):409-412.
10. Shoptaw S, Rotheram-Fuller E, Yang XW, et al. Smoking cessation in methadone maintenance. *Addiction.* Oct 2002;97(10):1317-1328.
11. Stein MD, Weinstock MC, Herman DS, Anderson BJ, Anthony JL, Niaura R. A smoking cessation intervention for the methadone-maintained. *Addiction.* Apr 2006;101(4):599-607.
12. Story J, Stark MJ. Treating cigarette-smoking in methadone-maintenance clients. *Journal of Psychoactive Drugs.* Apr-Jun 1991;23(2):203-215.
13. Okoli CTC, Khara M, Procyshyn RM, Johnson JL, Barr AM, Greaves L. Smoking cessation interventions among individuals in methadone maintenance: A brief review. *Journal of Substance Abuse Treatment.* Mar 2010;38(2):191-199.
14. Elkader AK, Brands B, Selby P, Sproule BA. Methadone-Nicotine Interactions in Methadone Maintenance Treatment Patients. *Journal of Clinical Psychopharmacology.* Jun 2009;29(3):231-238.
15. Richter KP, Hamilton AK, Hall S, Catley D, Cox LS, Grobe J. Patterns of smoking and methadone dose in drug treatment patients. *Experimental and Clinical Psychopharmacology.* Apr 2007;15(2):144-153.
16. Chait LD, Griffiths RR. Effects of methadone on human cigarette-smoking and subjective ratings. *Journal of Pharmacology and Experimental Therapeutics.* 1984;229(3):636-640.
17. Schmitz JM, Grabowski J, Rhoades H. The effects of high and low-doses of methadone on cigarette-smoking. *Drug and Alcohol Dependence.* Feb 1994;34(3):237-242.
18. Mello NK, Lukas SE, Mendelson JH. Buprenorphine effects on cigarette-smoking. *Psychopharmacology.* 1985 1985;86(4):417-425.
19. Mutschler NH, Stephen BJ, Teoh SK, Mendelson JH, Mello NK. An inpatient study of the effects of buprenorphine on cigarette smoking in men concurrently dependent on cocaine and opioids. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2002;4(2):223-228.
20. Mello NK, Mendelson JH, Sellers ML, Kuehnle JC. Effects of heroin self-administration on cigarette smoking. *Psychopharmacology (Berl).* Jan 1980;67(1):45-52.

21. Spiga R, Martinetti MP, Meisch RA, Cowan K, Hursh S. Methadone and nicotine self-administration in humans: a behavioral economic analysis. *Psychopharmacology*. Mar 2005;178(2-3):223-U221.
22. McCool RM, Richter KP. Why do so many drug users smoke? *Journal of Substance Abuse Treatment*. Jul 2003;25(1):43-49.
23. Chandra S, Shiffman S, Scharf DM, Dang Q, Shadel WG. Daily smoking patterns, their determinants, and implications for quitting. *Exp Clin Psychopharmacol*. Feb 2007;15(1):67-80.
24. Okie S. A flood of opioids, a rising tide of deaths. *N Engl J Med*. Nov 18 2010;363(21):1981-1985.
25. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med*. Nov 2 1995;333(18):1196-1203.
26. Johansson CJ, Olsson P, Bende M, Carlsson T, Gunnarsson PO. Absolute bioavailability of nicotine applied to different nasal regions. *Eur J Clin Pharmacol*. 1991;41(6):585-588.
27. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation - A randomized controlled trial. *Jama-Journal of the American Medical Association*. Jul 2006;296(1):47-55.
28. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha 4 beta 2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation - A randomized controlled trial. *Jama-Journal of the American Medical Association*. Jul 2006;296(1):56-63.
29. Poling J, Rounsville B, Gonsai K, Severino K, Sofuoglu M. The Safety and Efficacy of Varenicline in Cocaine Using Smokers Maintained on Methadone: A Pilot Study. *American Journal on Addictions*. Sep-Oct 2010;19(5):401-408.
30. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *J Consult Clin Psychol*. Feb 2000;68(1):134-144.
31. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry*. Mar 1986;43(3):289-294.
32. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13(3):293-308.
33. Morean ME, de Wit H, King AC, Sofuoglu M, Rueger SY, O'Malley SS. The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology (Berl)*. May 2013;227(1):177-192.
34. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict*. Sep 1991;86(9):1119-1127.
35. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. *Assessment*. Dec 2001;8(4):443-454.
36. West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology*. 2000;149(3):198-202.
37. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. Dec 2011;168(12):1266-1277.