Efficacy and Tolerability of Combination Varenicline With Hydroxyzine as a Potential Smoking Cessation Treatment (HAVE)

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Clinical Study Protocol

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PROTOCOL HISTORY

Date	Description
15 May 2019	Initial Version submitted to IRB on 24 May 2019
04 June 2019	Protocol Amendment 1: Clarification of follow up after dose adjustment (see Section 2.1 on page 9, Section 5.4 on page 18, and Section 6.3 on page 19). “Participants will be contacted with a follow-up call by Research Medical Staff within 72 hours of any dose adjustment.”

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APPENDIX

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ASP	Application Service Provider
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CC	Conventional cigarette
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CO	Carbon monoxide
CRF	Case report form
CRM	Customer relationship management
ECG	Electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
FTND	Fagerström test for nicotine dependence
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
ICF	Informed consent form

ICH	International Conference on Harmonisation
IRB	Institutional Review Board
Kg	Kilograms
Lbs	pounds
QTc	Corrected QT interval
mCEQ	Modified Cigarette Evaluation Questionnaire.
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
Mg	Milligram
mL	Milliliter
nAChR	Nicotinic Acetylcholine Receptor
MNWS	Minnesota Nicotine Withdrawal Scale
PHQ-9	The Patient Health Questionnaire
PPM	Parts per million
RBC	Red blood cell (count)
RCT	Randomized Control Trial
RRC	Rose Research Center, LLC.
SaaS	Software-as-a-Service
SAE	Serious adverse event
SMS	Short Message Service
SOP	Standard operating procedure
SSL	Secure Sockets Layer
STAI	State-Trait Anxiety Inventory
TLS	Transport Layer Security
V	Voltage
W	Wattage
WBC	White blood cell (count)

WHO	World Health Organization
WI-PREPARE	The Wisconsin Predicting Patients' Relapse Questionnaire

1 INTRODUCTION

1.1 STUDY DESIGN AND PLAN

This open-label study will evaluate hydroxyzine, a first-generation antihistamine, combined with varenicline, to help smokers abstain from smoking during a 12-week trial period by diminishing the nausea, stress, anxiety, and sleep disturbances associated with the use of varenicline and with nicotine withdrawal.

1.2 BACKGROUND

Cigarette smoking remains the leading cause of preventable death in the U.S., and is one of the leading causes of preventable morbidity and mortality.[1,2] An estimated 540,000 smokers die each year from smoking-related diseases.[3] Existing treatments for tobacco cessation yield, on average, less than 25% long-term abstinence rates, with many of the cessation failures occurring within the first month of abstinence.[4] There is an urgent need to develop new therapies for smoking cessation, including repurposing FDA-approved medications.[5] Current pharmacological approaches (e.g. nicotine replacement therapy, bupropion, or varenicline) increase efficacy for smoking cessation, but continue to have poor long-term abstinence rates, with potentially concerning adverse events.

Research into the predictors of smoking lapse, the initial step in smoking relapse and unsuccessful quit attempts, demonstrate the importance of stress as it relates to smoking cessation.[6] In 2011, McKee, et. al. demonstrated that stress decreases the ability to resist smoking.[7] An individual's response to stress from the discomfort of nicotine withdrawal and quitting smoking (so called "distress tolerance") may be an important factor in successful and persistent abstinence from smoking.[8] Additionally, sleep disturbances during smoking cessation, either as a withdrawal symptom from nicotine, or as a side effect of treatment medications (like varenicline), may play an important role in failed smoking cessation attempts.[9] One of the most successful medications, varenicline, a full agonist on α7-nicotinic acetylcholine receptors (nAChRs) and a partial agonist on the α4β2, α3β4, and α6β2 subtypes, has side effects which include nausea, difficulty sleeping, and nightmares.[10–12]

Hydroxyzine is an FDA approved first-generation antihistamine of the diphenylmethane and piperazine class that has antiemetic, anxiolytic, and sedative effects. Hydroxyzine's effects are primarily derived due to its actions as a potent H1 receptor inverse agonist. It also acts as an antagonist on the 5-HT2A, D2, and α1-adrenergic receptors. Because of its antiserotonergic effects, as well as the antagonistic effects on multiple receptor systems in the brain, hydroxyzine is noted to have strong anxiolytic properties, as well as mild antiobsessive and antipsychotic properties. Even with its effective sedative, hypnotic, and anxiolytic effects, hydroxyzine does not demonstrate any of the abuse, dependence, addiction or toxicity potential associated with medications within the same therapeutic range (such as benzodiazepines or nonbenzodiazepine hypnotics).[13]

In vitro studies point to the important role of H1 receptor antagonist (antihistamines) on the functional properties of cloned α7- nicotine acetylcholine receptor expressed in *Xenopus* oocytes.[14] Recent clinical trials have investigated antihistamines as potential aids in quitting smoking. This includes animal models which

evaluated the effects of the antihistamine pyrilamine (a centrally acting first-generation antihistamine) on Sprague-Dawley rats self-administering nicotine. This study showed significant reductions in nicotine self-administration with both acute dosing and repeated injections of this centrally acting antihistamine.[15(p1)] A recent study at Duke University evaluated meclizine (a first-generation nonselective H1 antagonist) as a potential smoking cessation treatment. In this phase II study completed in 2013, participants were given a divided dose of meclizine (either 25 mg a day or 50 mg a day, administered in two doses each day) with a nicotine patch for three weeks during the pre-quit period. The study results demonstrate the high potential for this class of medications to provide improved rates of abstinence for smokers who desire to quit.[16] As opposed to hydroxyzine, meclizine is not recognized to have anxiolytic properties, and has a much shorter half-live, only six hours, compared to hydroxyzine which has a half-life of about 20 hours.[17,18]

This study investigates the potential for decreasing the rate of adverse effects of varenicline and increasing the efficacy of varenicline when it is combined with hydroxyzine. Since hydroxyzine is an FDA-approved medication, marketed in the United States, it does not require an IND (Investigational New Drug) application. This study is not intended to support a new indication, support a change in labeling, support a change in advertising, nor does it involve a change in dosage level or route of administration.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 EFFICACY OF VARENICLINE AND HYDROXYZINE FOR STRESS AND SLEEP

A maximum of fifty (50) smokers will receive the FDA-approved dosing for both varenicline and hydroxyzine. These medications have been approved by the FDA for use by healthy, non-pregnant adults at the doses and frequencies specified in this study.

Participants enrolled in the study will take the FDA approved starter kit of varenicline for the first week of medication administration (0.5 mg nightly for days 1-3, then 0.5 mg twice daily for days 4-7). During the first week, participants will also receive hydroxyzine dosed in a similar manner, 50 mg nightly for the first 3 days, then twice daily, 25 mg in the morning and 50 mg at night. After the first week, participants will receive the FDA-approved dose of varenicline (1 mg twice daily) combined with hydroxyzine, 25 mg in the morning and 50 mg at nighttime. All medications will be dosed orally. The FDA has approved the 50 mg dose of hydroxyzine for treatment of nausea, anxiety, and insomnia. The morning dose of hydroxyzine is limited to 25 mg to minimize the sedative effects of this antihistamine, while the evening dose is prescribed at 50 mg to maximize the antiemetic, anxiolytic, and sedative properties. Dose adjustments for hydroxyzine by licensed medical providers may occur based on adverse effects reported by participants (e.g. daytime sedation…stop the AM dose of hydroxyzine, difficulty waking in the am…decrease nighttime dose of hydroxyzine). Participants will be contacted with a follow-up call by Research Medical Staff within 72 hours of any dose adjustment. Trial medications will continue until the participant returns for the End-of-Study visit, approximately 12 weeks after initiation of the medications.

2.1.1 Stress

Stress levels will be measured using the 10-item Perceived Stress Scale (PSS-10) at each laboratory session.

2.1.2 Anxiety and Depression

Anxiety levels and depression will be monitored using the 6-item State-Trait Anxiety Inventory (STAI) and the Patient Health Questionnaire (PHQ-9) provided during each laboratory sessions.

2.1.3 Additional Monitoring

Participants will respond to the Fagerström Test for Nicotine Dependence (FTND) and the Minnesota Nicotine Withdrawal Scale at each laboratory session after enrollment. Participants will also respond to the Modified Cigarette Evaluation Questionnaire (mCEQ, satisfaction with smoking) and the "Wisconsin Predicting Patients' Relapse" questionnaire (WI-PREPARE, susceptibility to smoking relapse) at Visit 2 and Visit 3. Spontaneous reduction in *ad libitum* smoking will be monitored with daily cigarette-use diaries, via SMS text messages. Data collection will begin upon enrollment and continuing until the End-Of-Study visit.

2.1.4 Side Effects and Tolerability data

Tolerability will be evaluated using open-ended as well as targeted side effect assessments at each visit. Participants will be queried on their level of nausea via daily SMS text messages.

2.2 Effects of Varenicline on Smoking Reduction prior to the Quit Date

Previous research has shown that abstinence at the end of treatment is strongly predicted by the extent to which smokers spontaneously reduce *ad libitum* smoking in the initial weeks of pharmacotherapy that is initiated before the quit-smoking date. This finding was initially discovered by the principal investigator (2009) using pre-quit date nicotine skin patch treatment and has been extended by other investigators who have found similar results using bupropion and varenicline. This early marker of subsequent success can be extremely useful in clinical practice by helping to guide adaptive changes in treatment before a potential relapse occurs. We will assess the extent of smoking reduction in participants during the initial seven days of treatment (prior to their planned quit date) through the End-Of-Study, indexed by smoking diaries and biochemical measures (expired air carbon monoxide). We will correlate these reductions with abstinence assessed at the end of treatment.

2.3 Identify Additional Early Predictors of Treatment Outcome

In addition to pre-quit reductions in ad libitum smoking, several other variables will be assessed in the first week before the quit-smoking date and correlated with end-of-treatment abstinence. These measures include: a) subjective ratings of the rewarding effects of smoking, craving for cigarettes and other nicotine withdrawal symptoms, assessed using standardized questionnaires; b) demographic measures, including gender, age, socioeconomic status, and race; and c) smoking history variables, including baseline cigarette consumption, level of nicotine dependence, and number of prior quit attempts.

2.3.1 Self-report of Smoking Behaviors and Nicotine dependence

Number of cigarettes smoked per day will be evaluated using daily diaries. Nicotine dependence measures will be taken using the Fagerström Test for Nicotine Dependence (FTND).[22]

2.3.2 Self-reported Rewarding / Aversive Effects of Cigarettes

Rewarding and aversive effects will be evaluated using the validated modified Cigarette Evaluation Questionnaire (mCEQ)[23], initially developed in the Principal Investigator's laboratory. The mCEQ assesses the degree to which participants experience the reinforcing effects of smoking, providing five subscale scores: smoking satisfaction (satisfying, tastes good, enjoy smoking), psychological reward (calms down, more awake, less irritable, helps concentrate, reduces hunger), aversion (dizziness, nauseated), enjoyment of respiratory tract sensations (single-item assessment), and craving reduction (single-item assessment).

3 INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This study design has been developed to hasten the identification and evaluation of promising new smoking cessation treatments. This single-group, small-scale, open-label study (N= maximum of 50) will evaluate hydroxyzine combined with varenicline. The rate of nausea reported in this study will be compared to the known nausea rates associated with varenicline alone (~30%). Interim data analysis will occur after 25 participants have reached the primary outcome. In choosing these thresholds, Monte Carlo simulations were conducted to determine the significance thresholds for both the N=25 and N=50 one-tailed binomial tests so that the overall false positive (Type I error) rate across all tests would be approximately 10%. Conversely, the overall false negative (Type II error) rate, whereby a promising treatment is discarded prematurely, would be approximately 20%. These initial results will fall into one of three categories:

3.1.1 Reported nausea 12% or less of participants

If three or less participants report nausea with combination hydroxyzine and varenicline, this investigational treatment will be viewed as having considerable promise and will immediately be advanced to a larger-scale (~N=200) randomized controlled clinical trial (RCT) and this “pilot” study will stop recruitment. This RCT will be submitted as a separate protocol.

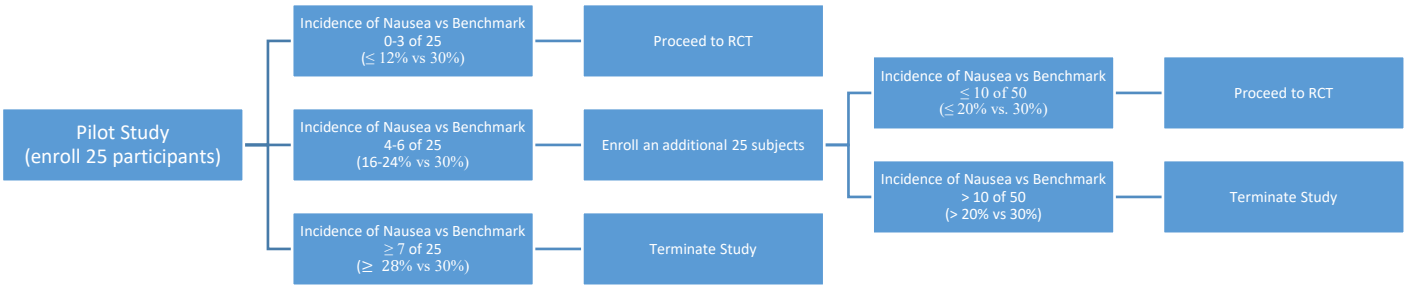
3.1.2 Reported nausea in 16% to 24% of participants

If 4 to 6 participants report nausea with combination hydroxyzine and varenicline, an additional 25 participants will be recruited to obtain a more precise estimate of the success rate. If, cumulatively, reported nausea is less than 20% (10/50), the combination of hydroxyzine and varenicline will be advanced to a larger-scale (~N=200) RCT.

3.1.3 Reported nausea in at least 28% of participants

If 7 or more participants report nausea with combination hydroxyzine and varenicline, this investigational treatment will be viewed unpromising and no additional participants will be enrolled.

3.1.4 Stepwise Evaluation Algorithm



3.2 Study Plan

After obtaining informed consent, adult smokers will be enrolled into the study. There will be an observational period of at least five days to obtain baseline data on use of combustible cigarettes and stress/anxiety and nausea symptoms.

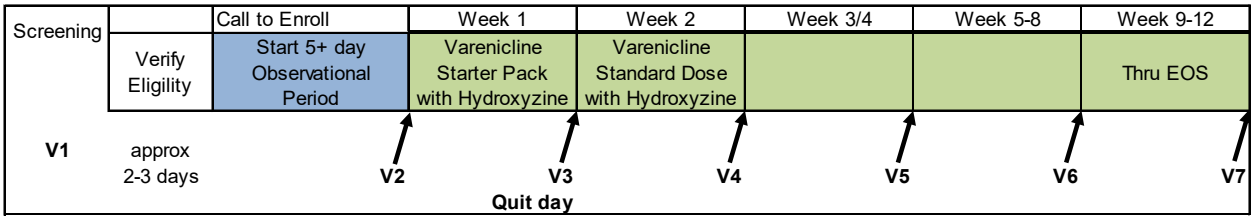


Figure 1 - Overall Study Design

Varenicline Dose = 0.5 mg QPM x 3 days, then 0.5 mg BID x 4 days, then 1.0 mg BID x 11 weeks
Hydroxyzine Dose = 50 mg QPM x 3 days, then 25 mg QAM + 50 mg QPM

3.3 Point of Enrollment

Participants will be enrolled after screening once all safety laboratory results have been received and reviewed by the medical staff (MD or PA). Study drugs will be dispensed starting at V2, and at each subsequent visit until the End-Of-Study.

3.4 Study and Session Durations

The expected duration of the study, from first participant, first visit, through last participant, last visit will be approximately one year. The total duration for a participant will be approximately 14-16 weeks.

- The Screening Session (Visit 1) will last approximately three hours.
- The other study sessions will last approximately one hour.

4 PARTICIPANT INVOLVEMENT

4.1 SELECTION OF STUDY POPULATION

Healthy, cigarette smoking adults, age 19-65 years, with no restriction on gender, race and ethnicities, or social-economic status, who have smoked an average of at least 10 commercially available cigarettes per day for the last 12 months will be screened for enrollment in this study.

The study will screen and enroll at both Rose Research Center locations, located in Raleigh and Charlotte, North Carolina.

4.1.1 Inclusion Criteria

Each participant must meet all the following inclusion criteria before enrollment:

Inclusion Criteria
1. Has signed the ICF and is able to read and understand the information provided in the ICF.
2. Is 19 to 65 years of age (inclusive) at screening.
3. Smokes at least 10 commercially available cigarettes per day for the last 12 months.
4. Has an expired air CO reading of at least 10 ppm at screening.
5. Express a desire to quit smoking within the next 30 days at screening.
6. Willing and able to comply with the requirements of the study.
7. Participant owns a smart phone with text message and data capabilities.

4.1.2 Exclusion Criteria

Potential participants who show or report indications of or self-report a diagnosis of conditions listed below may be excluded from the study. If the study physician (or designee) determines through the course of pre-screening, or a physical screen, medical history, physical findings, current medications, ECG, or laboratory findings suggests one of the conditions listed below, or findings reveal other information that may potentially jeopardize the participants' safe participation, then they may be excluded. For medical conditions that do not appear below, the participant may be enrolled if the study physician (or designee) does not feel that the medical condition would jeopardize safe study participation or data validity.

Exclusion Criteria
1. Is unhealthy or cannot participate in the study for any reason (e.g., medical, psychiatric, and/or social reason) as judged by the Investigator or designated medical staff based on all available assessments from the screening period (*e.g.*, safety laboratory, vital signs, physical examination, ECG, concomitant medications and medical history).
2. PHQ-9 score greater than 9, or a score greater than 0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way") at screening.
3. High blood pressure (systolic > 150 mmHg or diastolic >95 mmHg) at screening.

Exclusion Criteria
4. Body mass index (BMI) less than 15.0 kg/m^2 or greater than 40.0 kg/m^2.
5. Coronary heart disease, structural cardiac disease, cardiac dysrhythmias, abnormal ECG (e.g. prolonged QT_c), syncope, cardiac chest pain, or history of heart attack or heart failure.
6. Has received psychotherapy or behavioral treatments potentially impacting symptoms of depression, anxiety, or nicotine withdrawal within 30 days of screening, or during the study.
7. Taking antidepressants, psychoactive medications (e.g. antipsychotics, benzodiazepines, hypnotics) or medications that prolong QT_c.
8. Positive urine drug test for cocaine, THC, opiates, amphetamines or methamphetamines.
9. Use of smokeless tobacco (chewing tobacco, snuff), cigars, pipes, hookah, e-cigarettes, nicotine replacement therapy or other smoking cessation treatments within 14 days of enrollment.
10. Pregnant or nursing (by self-report) or has a positive pregnancy test.

4.1.3 Women of Childbearing Potential

Pregnant or breastfeeding women will be excluded from the study. All females will undergo a serum pregnancy test at screening (Visit 1) and a urine pregnancy test at each subsequent visit. Heterosexually active females of childbearing potential (not post-menopausal) must agree to use medically acceptable contraceptives during the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation, hysterectomy, or Essure), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B^{TM}, sold for emergency use after unprotected sex, are not acceptable methods for routine use. Female participants will be encouraged in the consent form to notify study staff if they believe a change in their pregnancy status has occurred during the trial.

Post-menopause is defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation).

4.2 Recruitment Strategies

Participants will be selected through IRB approved generic recruitment advertisements which are specifically designed to recruit participants into the volunteer database for future smoking and tobacco use related research at the Rose Research Center. For this database, many of the participants have provided basic smoking history data along with demographic information, which will allow selection of potentially interested participants.

Participants who call in will be screened into the volunteer database, and if they pre-qualify, will be offered the option to prescreen for this protocol.

Participants will be contacted only with IRB approved appropriate materials and information submitted along with this protocol. These documents will include a brief description of the study and information on how to prescreen for participation. Participants will be contacted by phone, email and text message prompting interested participants to prescreen through an electronic screen form.

4.2.1 Pre-Screening

Pre-screening will be completed prior to V1 for all participants. Participants will be provided with a set of IRB approved questions directly related to the inclusion and exclusion criteria. Based upon the outcome of these questions, potential participants may be scheduled for a screening visit (V1).

4.3 Participant Retention in the Study

All candidates who schedule a screening visit (V1) will receive a series of email, text, and telephone reminders; participants are also permitted through these communications to confirm, cancel, or reschedule all their appointments.

4.4 Discontinuation of Participants from Study

Discontinued participants will include both participants who withdraw from the study (participant's decision) or participants who are discontinued from the study (following Investigator's decision). A participant can only be discontinued from the study after enrollment. Participants that are not enrolled are considered screen failures.

Participants will be informed that they are free to withdraw from the study at any time. Participants should be questioned for the reason of premature withdrawal from the study, although they are not obliged to disclose it.

Participants discontinued from the study cannot re-enter the study.

4.4.1 Participants must be discontinued from the study for any of the following reasons:

- No-show to appointments and unable to reschedule within the visit window.
- Withdrawal of informed consent.
- Any adverse effect or condition that would jeopardize continued safe study participation.
- Pregnancy test is positive.
- Discontinuation is considered to be in the best interest for the participant or for other participants participating to the study, as judged by the Investigator or designee.

4.5 Lost to Follow-up

A reasonable number of attempts to contact the participant (including written correspondence and phone calls) should be made and documented in the source documents. The date of the last contact (e.g. last visit, last phone call) should also be recorded in the source document. When the PI(s) or designee(s) declare(s) a participant is lost to follow-up, the lost to follow-up date will be recorded and will correspond to the date of the end of study (EOS) of the participant.

4.6 Violation of Inclusion/Exclusion Criteria

Participants who, after signing the ICF, do not meet the inclusion and exclusion criteria will not be enrolled in the study and will be considered screen failures. Re-screening for the study is not permitted.

4.7 Participant Compensation

There will be a payment of $25 for the screening session, $50 for Visit 2 through Visit 6, and $100 for Visit 7. Participants will also receive payments of $5/day for responding to daily text messages.

If participants are asked by study staff to return to the Center to complete or redo parts of the sessions in situations of equipment malfunctions or other circumstances that are beyond the participants' control, participants may be reimbursed for mileage (based on the IRS's mileage rate).

Participants who decide to withdraw from the study will be paid for the part of the study they have completed.

4.8 Session and Response Windows

4.8.1 V2 Session Window

Participants may attend V2 up to 30 days post Screening Session (V1).

4.8.2 All other visit Windows

Participants may attend sessions up to four-calendar day's pre or post the scheduled visit.

4.8.3 SMS Response Window

The SMS response window will be open until the next SMS message is sent.

5 Hydroxyzine

5.1 Description of Hydroxyzine

Hydroxyzine is an FDA approved first-generation antihistamine of the diphenylmethane and piperazine class that has antiemetic, anxiolytic, and sedative effects. Hydroxyzine's effects are primarily derived due to its actions as a potent H1 receptor inverse agonist. It also acts as an antagonist on the 5-HT2A, D2, and α1-adrenergic receptors. Because of its antiserotonergic effects, as well as the antagonistic effects on multiple receptor systems in the brain, hydroxyzine is noted to have strong anxiolytic properties, as well as mild antiobsessive and antipsychotic properties. Even with its effective sedative, hypnotic, and anxiolytic effects, hydroxyzine does not demonstrate any of the abuse, dependence, addiction or toxicity potential associated with medications within the same therapeutic range (such as benzodiazepines or nonbenzodiazepine hypnotics).[13]

LLorca et al. demonstrated the safety and efficacy of hydroxyzine in the treatment of generalized anxiety disorder.[20] A common adverse event for hydroxyzine (occurring 10% or more) is drowsiness. All other adverse events occurred less than 10% or were of unknown incidence. This includes dry mouth, cough, unusual tiredness, and irregular or slow heart rate.[21]

A Cochrane Review from 2014 which looked at interventions for nausea and vomiting in early pregnancy noted that hydroxyzine had a statistically significant improvement in nausea at a dose of 25 mg twice a day, when compared with placebo (see figure 2).[24] It also noted that only 7% of the participants using hydroxyzine reported only "slight drowsiness" while taking this medication at this particular dose.[24] No other adverse effects were reported in this review.

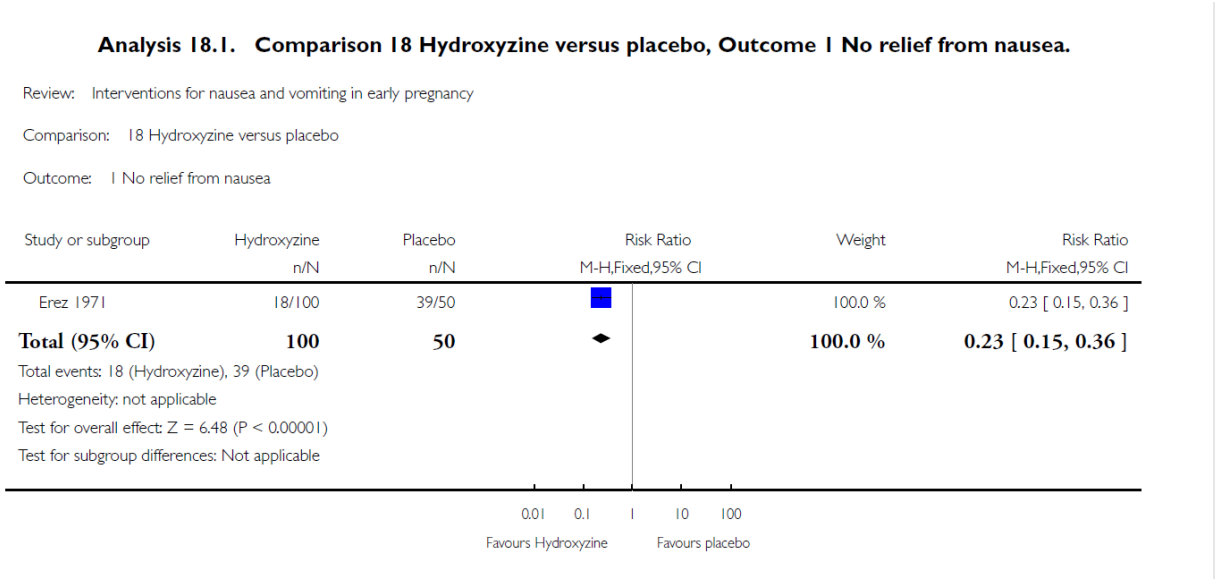


Figure 2: From Matthews A, Haas DM, O'Mathúna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2015;(9):CD007575. doi:10.1002/14651858.CD007575.pub4

A study published in 2012 evaluated the efficacy of combining hydroxyzine with ondansetron for treatment of side effects associated with chemotherapy regiments which utilized highly emetogenic drugs. This study demonstrated that complete control of acute emesis was achieved in 56% of pediatric cancer patients utilizing both antiemetic medications versus only 22% utilizing ondansetron without hydroxyzine (p=0.006).[25] This study also reported that patients and parents noted "…significantly better sleeping quality, appetite, activity and mood…" for those patients taking ondansetron with hydroxyzine versus without hydroxyzine. The dose of hydroxyzine used was 1 mg/kg/dose, equivalent to 77 mg for an average adult female and 89 mg for an average adult male (an average American female weighs 170 lbs. and an average American male weighs 197 lbs. according to the CDC).[26] Dosing for this study will be based on minimizing the risk of sedation (25 mg AM dosing) while optimizing the beneficial effects of the study drug (50 mg PM dosing). Participants will be titrated to these doses in a similar fashion as the titration of varenicline, allowing for dose adjustment based on daily evaluation of potential side effects.

5.2 Hydroxyzine Product Use Timeframe

Dosing will begin one week before a target quit-smoking date and will continue for a total of approximately 12 weeks, the same duration as the FDA-approved dosing for varenicline. Since hydroxyzine does not demonstrate any dependence or addictive properties, there is no indication to taper the dose.

5.3 Dosage

- First 3 days of treatment: PM – two 25 mg tablet orally.
- Starting on the fourth day of treatment and continuing until the EOS: AM – one 25 mg tablet orally; PM – two 25 mg tablets orally.
- Dosing will be adjusted based on reported side effects.

5.4 Dose Adjustment Procedures

Dose adjustments for hydroxyzine will be performed by licensed medical providers based on adverse effects reported by participants (e.g. daytime sedation…stop the AM dose of hydroxyzine, difficulty waking in the am…decrease nighttime dose of hydroxyzine). Participants will be contacted with a follow-up call by Research Medical Staff within 72 hours of any dose adjustment.

5.5 Accountability and Compliance

5.5.1 Dispensing Product

The hydroxyzine will be dispensed by the Investigator or designated study staff utilizing blister-pack technology to enhance compliance and accountability. Each dispense and collection of the product will be recorded during each laboratory visit (Visit 2 through Visit 6). All study-related drugs will be expected to be returned by the participant at the End-Of-Study (Visit 7 or early termination).

Prior to dispensing, the site will ensure that the product packaging is labelled with the protocol number and unique participant identifiers, date it was dispensed, and the statements “For investigational use only” and “Keep out of reach of children”.

5.5.2 Storage and Accountability

Hydroxyzine will be stored in a climate-controlled secured-storage site (15 degrees C to 30 degrees C) with access limited to authorized personnel only. Full accountability of the distributed products will be ensured by designated staff.

5.5.3 Compliance

Compliance will be ensured by strict distribution of the product, daily SMS messages, and collection of unused products at each study session. This information will be documented in appropriate logs.

6 Varenicline

6.1 Description of Varenicline

Varenicline is one of two FDA-approved non-nicotine medications prescribed as a smoking cessation aid. It is a partial agonist of the α4β2 nACHR. Due to its relatively long half-life, compared to nicotine, varenicline also acts as an antagonist, blocking occupied receptors from additional stimulation from nicotine. Recognized as one of the most effective monotherapy treatments for tobacco dependence, the medication increases the odds of quitting smoking by nearly fourfold compared with placebo. Hays et al. found varenicline to be generally safe and well tolerated as a smoking cessation aid. Common adverse events associated with varenicline (occurring 10% or more) include nausea, insomnia, abnormal dreams, headaches, and nasopharyngitis.[19] Nausea, the most common side effect of varenicline, has been reported as high as 30%. Abnormal dreams and insomnia have been reported by over 10% of users.[27–29]

6.2 Dosage

- 0.5 mg tablet orally once a day for 3 days.
- Starting on the fourth day, 0.5 mg tablet twice a day, orally.

- After one week, 1.0 mg tablet twice a day, orally.

6.3 Dose Adjustment Procedures

Dose adjustments for varenicline will be performed by licensed medical providers based on adverse effects reported by participants (e.g. insomnia, abnormal dreams, mood disturbances, anxiety…decrease dose to 0.5 mg twice a day for moderate to severe side effects). Participants will be contacted with a follow-up call by Research Medical Staff within 72 hours of any dose adjustment.

6.4 Accountability and Compliance

6.4.1 Dispensing Product

The varenicline will be dispensed by the Investigator or designated study staff utilizing blister-pack technology to enhance compliance and accountability. Each dispense and collection of the product will be recorded during each laboratory visit (Visit 2 through Visit 6). All study-related drug will be collected at the End-Of-Study (Visit 7 or early termination).

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Compliance will be ensured by strict distribution of the product, daily SMS messages, and collection of unused products at each study session. This information will be documented in appropriate logs.

7 Study Procedures and Activities

Personnel performing study assessments must have appropriate and documented training. An overview of all study assessments is shown in the schedule of events (Section 8.5). Study personnel will adhere to standard operating procedures (SOPs) for all activities. Appropriate medical advice will be provided to the participant in case of any medical findings requiring health care.

7.1 Informed Consent and Guidance

Prior to any study assessments being performed, the participant will be asked to provide their written consent to participate in the study on an informed consent form (ICF). All assessments must start after the time of ICF signature by the participant.

Designated staff will obtain written consent from each participant under the supervision of the Principal Investigator. The person obtaining consent provides the participants with a written document explaining the procedures and risks and will answer any questions. A signed copy of the informed consent form will be given to

each participant. Participants are informed that they may withdraw from participation in the study at any time without penalty.

Because of the nature of this study and the number of questionnaires that participants are expected to complete, we do not recruit potential participants who do not read, are blind or who do not read/understand English. We are not equipped to validate alternate versions of our questionnaires. Questionnaires cannot be administered orally by a translator or by technicians to illiterate or blind participants because the data obtained would not be comparable to self-administered questionnaires.

7.2 Safety Laboratory and Other Assessments

An overview of all assessments is provided in the schedule of events (Section 8.5).

Non-fasting blood samples and urine samples will be collected by qualified and trained site personnel. Participants will be in a seated or in a supine position during blood collection.

The maximal total volume of blood drawn for each participant will be 12.5 ml for clinical chemistry, hematology, and serum pregnancy (for females only).

Samples for clinical chemistry, hematology, urinalysis, and serum pregnancy test will be sent to a central laboratory for analysis. Urine pregnancy and urine drug testing will be performed on-site.

The results of the clinical chemistry, hematology and urinalysis safety panel will not routinely be given to participants. However, if the participant's laboratory results are clinically relevant (including positive pregnancy tests), the medical staff will send the participant a copy of the laboratory results. Participants who are accepted into the study but need medical follow up due to minor abnormalities in laboratory results will also receive a copy of the laboratory results.

7.2.1 Blood Samples

Blood samples will be collected by qualified and trained site personnel. Participants should be in a seated or supine position during blood collection.

The maximal total volume of blood drawn for each participant will be around 12.5 mL for safety analysis. Samples will be sent to an external laboratory for testing.

Hematology
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin concentration (MCHC)
Hematocrit
Red blood cell (RBC) count
Differential WBC count
Platelet count
Hemoglobin
Mean corpuscular hemoglobin (MCH)
White blood cell (WBC) count

Clinical Chemistry	
Sodium	Potassium

Chloride	Carbon Dioxide
Blood Urea Nitrogen	Creatinine
Glucose	Total Protein
Albumin	Total Bilirubin
Alkaline Phosphatase	Alanine aminotransferase (ALT)
Estimated Glomerular Filtration Rate	Aspartate aminotransferase (AST)
Calcium	

Table 1 - Clinical Chemistry & Hematology Assessments

7.2.2 Serum Pregnancy Test

Serum pregnancy test will only be performed during the screening visit for all female participants

Serum Pregnancy Test
Qualitative human chorionic gonadotropin (HCG) test

Table 2 – Serum Pregnancy Test

7.2.3 Urine Samples

Urine samples will be collected for the urine drug screen (at screening session), urine pregnancy test (at all sessions except screening), and safety urinalysis (at screening session). The urine drug screen and pregnancy tests will be performed by study personnel at the study site. The urine sample collected for urinalysis will be sent to an external laboratory for testing.

In case of any positive pregnancy test, the Investigator or designee will inform the participant about the risks associated with smoking during pregnancy.

Urinalysis
pH
Red blood cell traces
Bilirubin
Protein
Glucose
Specific gravity
Nitrite
WBC Esterase

Table 3 - Urinalysis Assessments

Drug Screening
Amphetamine
Cocaine
THC
Methamphetamine
Opiates

Table 4 - Drug Screening

7.2.4 Urine Pregnancy Test

The urine pregnancy tests will be performed by study personnel at RRC. Urine pregnancy tests will be performed for all females at all visits except screening.

7.2.5 Expired Air CO Breath Test

Carbon Monoxide (CO) in participant's exhaled breath (expressed as ppm) will be measured using a Vitalograph CO Monitor. Participants must have an expired air CO reading at V1 of at least 10 ppm for inclusion into this study. This test will be repeated at each of the laboratory sessions.

7.2.6 Medical History and Concomitant Disease

Relevant medical history and concomitant disease will be documented at the screening visit (V1). Medical history is defined as any condition that started and ended prior to V1. A concomitant disease is defined as any condition that started prior to V1 and is still ongoing at V1 (this may also include findings detected during the screening visit).

7.2.7 Prior and Concomitant Medication

All medication taken four weeks prior to the screening visit (V1) and during the study will be documented using a source document. Medications which are stopped before V1 will be considered as prior medication. Medication which was started prior to V1 and which is still being taken by the participant during the study as well as medication that is initiated after V1 will be considered as a concomitant medication. This applies to both prescription and over-the-counter products (e.g., vitamins).

Records of prior and concomitant medications taken include the drug name (preferably both generic and trade name), route of administration, dose/unit, frequency of use, indication, the start and if applicable, the stop date. Any therapy changes (including changes of regimen) during the study will be documented.

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system. The timing of these questionnaires is outlined in the Schedule of Events 8.5.

7.2.8 Demographics

Sex, date of birth, race and ethnicity will be recorded for each participant according to Section 8.5.

7.2.9 Height and Weight

Height and weight will be measured and recorded according to Section 8.5.

7.2.10 Physical Examination

A physical examination will be performed according to Section 8.5. The physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, chest, abdomen, dentition, cardiovascular, musculoskeletal and neurological systems. The physical examination is to be conducted by a designated fully trained and licensed medical staff.

Appropriate medical advice will be provided to the participant if any medical findings requiring health care are identified.

7.2.11 AE/SAE Reporting

AEs/SAEs will be assessed using questionnaires and face-to-face interviews at the indicated time points and spontaneous reporting from the time of ICF signature until the EOS for the participant (see Section 8.5).

7.2.12 Electrocardiogram (ECG)

ECG recording will be performed as per RRC Standard Operating Procedures at screening. A standard 12-lead ECG will be recorded after the participant has rested for at least 5 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval (Bazett). Every ECG will be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

ECG printouts will be interpreted by a qualified physician or physician assistant. Any printouts of ECGs on thermo-sensitive paper will be photocopied and stapled together for inclusion in the source documents and signed by the qualified physician or physician assistant.

7.2.13 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate and respiratory rate), will be measured in sitting position after the participant has rested for at least 5 minutes according to Section 8.5. At the screening visit, blood pressure and heart rate will be measured again at least two minutes later in a standing position.

7.2.14 Questionnaires

The questionnaires will be administered to the participants using paper questionnaires and/or an electronic data collection system. The questionnaires will be asked according to Section 8.5.

7.2.14.1 *10-Item Perceived Stress Scale (PSS-10)*

Self-report questionnaires are the simplest method for obtaining a rapid evaluation of a participant's realized stress levels. The Perceived Stress Scale (PSS) was developed in 1983 as a psychometrically valid measure of perceived stress. A 2011 study reviewed the use of the PSS in a sample of participants who smoked, evaluating three different versions; the PSS-14 (14-item questionnaire), the PSS-10 (10-item questionnaire), and the PSS-4 (4-item questionnaire). The results from this 2011 study confirmed the psychometric properties of all three versions.[30] Our study will utilize the PSS-10 during all visits after enrollment (V2 through V7) to evaluate self-reported perceived stress levels.

7.2.14.2 *6-Item State-Trait Inventory (STAI)*

In 2011, Dr. Laura Julian from University of California, San Francisco, published a review of available validated methods for accurately measuring anxiety. Her review focused on self-reported measures of general anxiety. She reviewed three different models; the State-Trait Anxiety Index, the Beck Anxiety Inventory, and the anxiety subscale of the Hospital Anxiety and Depression Scale. The STAI demonstrated excellent reliability and good validity, and is both responsive and sensitive to change.[31,32] The STAI is among the most widely used measures of general anxiety. Our study will utilize the 6-item STAI during all visits after enrollment (V2 through V7) to evaluate self-reported anxiety levels.

7.2.14.3 ***PHQ-9 -- The Patient Health Questionnaire***

The Patient Health Questionnaire PHQ-9 for Depression will be used to screen for current (within 2 weeks) depression. Potential participants who score >9 (or who score >0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way")) will be excluded from study participation, and, at the discretion of the study physician/physician assistants, referred to appropriate psychiatric treatment. Participants will respond to this questionnaire at all visits. This questionnaire will be administered at every visit, including the screening visit (V1 through V7).

7.2.14.4 *Modified Cigarette Evaluation Questionnaire (mCEQ)*

The mCEQ assesses the degree to which participants experience the reinforcing effects of smoking. This questionnaire will be administered after enrollment and prior to commencing the investigational products (V2 and V3).

7.2.14.5 *MNWS –Minnesota Nicotine Withdrawal Scale*

The MNWS will be used at all visits after "quit day" (V4 through V7) to assess nicotine withdrawal symptoms including craving and mood effects. Participants will be asked to assess the following seven symptoms (on a 5-point scale ranging from 0 to 4, where 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe):

- Desire or craving to smoke
- Anger, irritability, frustration
- Anxiety or nervousness
- Difficulty of concentrating
- Impatience, restlessness
- Hunger
- Depression

7.2.14.6 ***FTND -- The Fagerström Test for Nicotine Dependence***

The Fagerström Test for Nicotine Dependence is a six-item questionnaire developed by Karl-Olov Fagerström and is used to determine someone's level of nicotine dependence. The scores obtained on the test allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7 -10 points). This questionnaire will be given at all visits (V1 through V7).

7.2.14.7 ***WI-PREPARE – Wisconsin Predicting Patients' Relapse Questionnaire***

The WI-PREPARE is a seven-item questionnaire that is designed to assess a participant's susceptibility to smoking relapse. The questionnaire includes measures of physical dependency, environmental factors and smoking characteristics. Participants will respond to this questionnaire after enrollment and prior to the selected "quit day" (V2 and V3).

7.2.14.8 ***Prior and Concomitant Medication***

At each visit, participants will report any changes in medication use, including the use of supplements, vitamins, over-the-counter medications, and prescription medications.

7.2.14.9 ***Smoking History Questionnaire***

The Smoking History is a questionnaire designed to help assess the participant's current and past smoking habits. This questionnaire will be administered at screening (V1) and will include questions about the number of years participants have smoked combustible cigarettes (CC), the number of CCs per day smoked over the last 12 months, brand of CCs, use of other tobacco products and use of nicotine replacement therapy or other smoking cessation treatments. This questionnaire will also be used to check eligibility criteria.

7.2.14.10 ***Registration Form***

This form is an internal questionnaire designed to collect demographic information about participants. It will be administered at screening (V1).

7.2.14.11 ***Medical History Form***

The Medical History form is an internal questionnaire designed to help assess the participant's current health and any health history. This questionnaire also includes questions about all medications (include prescription medications, other-the-counter medications or supplements) taken in the past 30 days. It is designed to help assess the participant's current health and health history and is used to help determine eligibility. This form is administered at the initial screening visit (V1).

7.2.14.12 *Review of Systems*

The Review of Systems is an internal questionnaire administered at screening (V1) to help assess the participant's current health and health history by asking about the presence of a list of symptoms.

7.2.14.13 *Employment History*

The Employment History is an internal questionnaire designed to collect information about a participants' social economic status. Participants will be presented this questionnaire after enrollment, at the second visit (V2).

7.2.14.14 *Adverse Effects*

During each visit after enrollment (V2 through V7), participants will respond to adverse events based on a mild/moderate/severe rating. The questionnaire will use both targeted questions and open-ended questions to access for any adverse effects/events. Participants will respond to SMS text message inquiries for study specific adverse effects, on a daily basis, commencing after enrollment (see Section 8.8).

7.2.14.15 *Medication Compliance*

Participants will be queried via SMS text messages whether they have been compliant with taking the study specific medications. These messages will commence after the second visit and continue through the End of Study (see Section 8.8).

7.2.14.16 *Smoking Status*

SMS text messages will be sent to participants starting after enrollment, through the End of Study, to ascertain the participants smoking status (see Section 8.8).

8 SESSIONS

8.1 SCREENING SESSION (V1)

Eligibility of participants to participate in this study will be assessed at the screening visit (V1). The ICF will be signed, dated and timed prior to any other screening procedures (see Section 8.5).

The sequence of the following assessments will be at the discretion of the Investigator (or designee) after signature of the ICF.

- Questionnaires
    - Smoking History
    - Registration Form
    - Medical History (with Review of Systems)
    - Patient Health Questionnaire (PHQ-9)
- Prior and Concomitant Medication
- Expired air CO breath test
- Urine collection for urinalysis and drug screen
- Vital signs (blood pressure, heart rate, respiratory rate)
- Height and weight / BMI
- Temperature
- Electrocardiogram (ECG)
- Physical examination

- Blood collection for safety laboratory testing (including pregnancy test for females)
- Instructions on use of the SMS messaging/questionnaire system

8.2 5-DAY OBSERVATION PERIOD

After verification of eligibility (approximately two days after screening), participants will be enrolled in the study and commence a five-day observational period. Participants will be called and given instructions on the use of the SMS system which will administer questions about adverse effects and smoking status in order to collect baseline data prior to start of the study drugs.

8.3 PRE-QUIT SESSION (V2)

After completion of a minimum five-day observational period, participants will come to the Center for assessment, training (including brief quit smoking counseling), and dispensing of study drugs. The quit date will be scheduled for the day after Visit 3, and seven days after commencing the study drugs. The sequence of the following assessments will be at the discretion of the Investigator or designee.

- Document concomitant disease and medication changes
- Physical examination (if indicated)
- Expired air CO breath test
- Vital signs (blood pressure, heart rate, respiratory rate)
- Weight
- Brief smoking cessation counseling (QuitAssist Counseling Handout)
- Urine pregnancy test (all females)
- Dispensing of study drugs
- Verification of proper use of the SMS messaging (refresher training, if needed)
- Questionnaires
    - Employment History
    - FTND
    - PSS-10
    - 6-Item STAI
    - Adverse Effects Questionnaire
    - Patient Health Questionnaire (PHQ-9)
    - Wisconsin-Predicting Patient's Relapse (WI-PREPARE)
    - Modified Cigarette Evaluation Questionnaire (mCEQ)
    - Smoking Status (daily via SMS survey, commence after visit)
    - Medication Compliance (daily via SMS survey, commence after visit)

8.4 DAY BEFORE QUIT DATE (V3)

Six days after starting medications (one day prior to quit date), participants will return to the Center for assessment and collection/dispensing of study drugs. The sequence of the following assessments will be at the discretion of the Investigator or designee.

- Document concomitant disease and medication changes
- Physical examination (if indicated)

- Expired air CO breath test
- Vital signs (blood pressure, heart rate, respiratory rate)
- Weight
- Brief review of smoking cessation counseling (if indicated)
- Urine pregnancy test (all females)
- Collection and dispensing of study drugs
- Assess medication compliance
- Verification of proper use of the SMS messaging (refresher training, if needed)
- Questionnaires
    - FTND
    - PSS-10
    - 6-Item STAI
    - Adverse Effects Questionnaire
    - Patient Health Questionnaire (PHQ-9)
    - Wisconsin-Predicting Patient's Relapse (WI-PREPARE)
    - Modified Cigarette Evaluation Questionnaire (mCEQ)
    - Smoking Status (review with participant and continue daily via SMS survey)
    - Medication Compliance (review with participant and continue daily via SMS survey)

8.5 POST-QUIT SESSIONS (V4-V7)

Sessions scheduled after the quit-smoking date will be conducted at 2 weeks after the quit date and then at 4-week intervals until the end of the 12-week treatment period. The sequence of the following assessments will be at the discretion of the Investigator or designee.

- Document concomitant disease and medication changes
- Physical examination (if indicated)
- Expired air CO breath test
- Vital signs (blood pressure, heart rate, respiratory rate)
- Weight
- Brief review of smoking cessation counseling (if indicated)
- Urine pregnancy test (all females)
- Collection and dispensing of study drugs (collection only at the EOS visit)
- Assess medication compliance
- Verification of proper use of the SMS messaging (refresher training, if needed)
- Questionnaires
    - FTND
    - PSS-10
    - MNWS
    - 6-Item STAI
    - Adverse Effects Questionnaire
    - Patient Health Questionnaire (PHQ-9)
    - Smoking Status (review with participant and continue daily via SMS survey until End of Study)
    - Medication Compliance (review with participant and continue daily via SMS survey until End of Study)

8.6 6-Month Follow Up

Participants who successfully complete the study and are abstinent at the final visit (V7), will be contacted six months after the quit day utilizing an automated SMS messaging system, to ascertain their current smoking status.

8.7 Schedule of Events

Visit Assessments and Procedures		Screening Session	5-day observation period	Laboratory Sessions						6-month f/u
		V1		V2	V3	V4	V5	V6	V7	
	Informed Consent and Guidance	•								
	Inclusion/Exclusion Criteria	•								
	Enrollment		•*							
	Prior and Concomitant Medication	•		•	•	•	•	•	•	
Questionnaires	Smoking History Questionnaire	•								
	Registration Form	•								
	Employment History			•						
	Medical History/Review of Systems	•								
	10-item Perceived Stress Scale (PSS-10)			•	•	•	•	•	•	
	6-Item State-Trait Inventory			•	•	•	•	•	•	
	Wisconsin-Predicting Patient's Relapse (WI-PREPARE)			•	•					
	Modified Cigarette Evaluation Questionnaire (mCEQ)			•	•					
	The Fagerström Test for Nicotine Dependence (FTND)			•	•	•	•	•	•	
	Patient Health Questionnaire (PHQ-9)	•		•	•	•	•	•	•	
	Minnesota Nicotine Withdrawal Scale (MNWS)					•	•	•	•	
	Smoking Status (via daily SMS text)		•	•	•	•	•	•	•	•
	Medication Compliance (via daily SMS text)			•	•	•	•	•	•	
	Adverse Effects Questionnaire (at visits and daily SMS Text)		•	•	•	•	•	•	•	
	Safety Laboratories	•								
	Serum Pregnancy Test (Females)	•								
	Urine Pregnancy Test (Females)			•	•	•	•	•	•	
	Urine Drug Screen	•								
	CO Breath Test	•		•	•	•	•	•	•	
	ECG	•								
Vitals	Blood Pressure	•		•	•	•	•	•	•	
	Heart rate	•		•	•	•	•	•	•	
	Temperature	•								
	Respiratory rate	•		•	•	•	•	•	•	
	Weight	•		•	•	•	•	•	•	
	Height	•								
	BMI	•								
	Physical Examination	•		•#	•#	•#	•#	•#	•#	
	Collect Used/Unused Blister Packs				•	•	•	•	•	
	Dispense Study Drugs in Blister Packs			•	•	•	•	•		

*After evaluation of safety labs, prior to start of observational period

Targeted examination as needed

8.8 SMS MESSAGING

8.8.1 Daily SMS Message (after enrollment, prior to V2) – Participants will receive a text with a link to a survey to access the following:

- How soon after you wake up did you smoke your first cigarette?
  1-Within 5 Minutes, 2-6 to 30 Minutes, 3-31 to 60 Minutes, 4-After 60 Minutes
  - How many cigarettes did you smoke today?
  - What was your level of stress today?
    1-No Stress, 2-Mild Stress, 3-Moderate Stress, 4-A Lot of Stress, 5-Extreme Stress
  - How well did you sleep last night?
    1-No problems, 2-Mild problems, 3-Moderate problems, 4-A Lot of problems, 5-Extreme problems
  - Did you feel nauseated today?
    1-No nausea, 2-Mild nausea, 3-Moderate nausea, 4-A lot of nausea, 5-Extreme nausea

8.8.2 Daily SMS Message (after Visit 2) -- Participants will receive a text with a link to a survey to assess the following:

- Have you smoked any cigarettes today?
  - If yes, how soon after you wake up did you smoke your first cigarette?
    1-Within 5 Minutes, 2-6 to 30 Minutes, 3-31 to 60 Minutes, 4-After 60 Minutes
  - How many cigarettes did you smoke today?
- Did you take your study drugs this morning?
- Did you take your study drugs this evening?
- What was your level of stress today?
  1-No Stress, 2-Mild Stress, 3-Moderate Stress, 4-A Lot of Stress, 5-Extreme Stress
- How well did you sleep last night?
  1-No problems, 2-Mild problems, 3-Moderate problems, 4-A Lot of problems, 5-Extreme problems
- Did you feel nauseated today?
  1-No nausea, 2-Mild nausea, 3-Moderate nausea, 4-A lot of nausea, 5-Extreme nausea

8.8.3 6-Month follow up SMS Message -- Participants will receive a text with a link to a survey to assess the following:

- Have you smoked a cigarette since your last visit?
  - If yes, are you still smoking cigarettes right now?

9 RISK / BENEFIT INFORMATION

9.1 POTENTIAL BENEFITS

The participants will be encouraged to quit smoking, which would significantly reduce their risk of smoking-related diseases.

9.2 Importance of Knowledge to be Gained

By conducting the proposed research, we may develop a new approach to smoking cessation treatment that promises to help a significantly larger proportion of smokers to quit successfully. This would have a major positive impact on public health.

9.3 Potential Risks

Continuing to smoke carries significant health risks; if participants are successful at maintaining abstinence (and possibly quit), the participants in the studies will realize a significant improvement in their health and a decrease in their risk of morbidity and mortality associated with smoking combustible cigarettes.

9.3.1 Hydroxyzine

Hydroxyzine is a first-generation antihistamine which has FDA-approval as an antiemetic, anxiolytic, and sedative medication. Even with its effective sedative, hypnotic, and anxiolytic effects, hydroxyzine does not demonstrate any of the abuse, dependence, addiction or toxicity potential associated with medications within the same therapeutic range (such as benzodiazepines or nonbenzodiazepine hypnotics).[13] A common adverse event for hydroxyzine (occurring 10% or more) is drowsiness. All other adverse events occurred less than 10% or were of unknown incidence. This includes dry mouth, cough, unusual tiredness, and irregular or slow heart rate.[21] Studies of hydroxyzine have shown a lack of organ toxicity and absence of dependence. Case reports of QT prolongation and Torsade de Pointes have been reported during post-marketing analysis. These reports were noted to occur in patients with other risk factors for QT prolongation.

9.3.2 Varenicline

Varenicline is one of the most widely used prescription medications for smoking cessation. Common adverse events associated with varenicline include nausea, insomnia, abnormal dreams, headaches, and nasopharyngitis.[19] The most common adverse reaction reported is nausea, with 30-40% of participants in randomized control trials reporting mild to moderate levels of nausea.[33] Discontinuation/drop-out rates of nearly 10% have been noted during clinical trials due to these adverse effects.[34] In addition to the potential drug-specific side effects noted, any medication may trigger a serious allergic reaction and may cause shock, seizures (convulsions, epilepsy, "fits"), loss of consciousness, tingling, swelling of the face, lips, tongue, throat and/or vocal cords, difficulty breathing, asthma, wheezing, rash, hives, itching, and possibly death.

9.3.3 Nicotine Withdrawal

Participants may experience nicotine withdrawal symptoms, including craving, difficulty concentrating, nausea, insomnia, headache, mood disturbance and increased appetite/weight gain.

9.3.4 Blood Draw

The risks associated with venipuncture are minimal and include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

9.4 Protection Against Risks

Participants will be screened medically and monitored throughout the study. Participants will be instructed to report any side effects to study staff, who will communicate these reports immediately to the medical staff. The most appropriate course of action will be determined, which may include options for dose reduction or termination of treatment. Participants whose treatment is terminated will be encouraged to remain in the study for assessment of outcomes and to receive continuing social support for quitting smoking. Participants will, however, be reminded that they have the option to withdraw from the study at any time. Participants will also be given the 24-hour emergency contact number in the event that side effects or adverse events occur between sessions.

9.4.1 Blood Pressure Monitoring

After study enrollment, if blood pressure during laboratory visits is above 160/100, then the following actions will be taken to enhance participant safety:

- If BP >210/120 with symptoms of malignant hypertension, all experimental interventions will be stopped immediately, and the participant will be referred to appropriate medical treatment. Participation may resume, with continued monitoring, if BP is no greater than 150/100.
- If BP > 160/100 for 2 consecutive sessions, the Center will request that the participant have their BP checked weekly by their PCP, local pharmacy, or home machine and call us with results. Participants will also be encouraged to see their PCP regarding evaluation, treatment, and further monitoring.

10 Quality Control and Quality Assurance

10.1 Training of Staff

The Investigator or designee will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff.

10.2 Audits and Inspections

Good Clinical Practice regulations require independent inspections of clinical program activities. Such inspections may be performed at any time before, during, and after the study.

Authorized representatives of the Sponsor, regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported, according to the protocol, ICH/GCP guidelines and any applicable regulatory requirements. The Investigator or designee will contact the Sponsor immediately if contacted by a regulatory agency about an inspection at their site.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by the Sponsor, its authorized representative, and other regulatory agencies.

11 REPORTING OF ADVERSE EVENTS

11.1 DEFINITIONS

11.1.1 Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence that may present during participation in the study and which may or may not have a causal relationship with study procedures and/or products tested in this study. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study procedures and/or products.

Any increase in the severity and/or the frequency of a concomitant disease is considered an AE.

11.1.2 Serious Adverse Event

A Serious Adverse Event is any adverse event that:

- results in death;
- is life-threatening;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity;
- results in a congenital anomaly / birth defect;
- requires immediate medical or surgical intervention.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based on appropriate medical judgment, the event may jeopardize the participant, or the participant may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

Any pre-planned hospitalizations that are known at the time of signing the ICF will not be recorded as an SAE; however, they will be recorded as AE only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

11.2 COLLECTION OF SAFETY EVENTS FROM PARTICIPANTS

Information recorded when collecting AEs will include: thorough description of the AE, seriousness assessment, start and stop dates (if known), circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence, the action taken with the investigation

product/procedures due to the AE, the participant`s disposition in the study after the occurrence of the AE and the final outcome of the AE (if known).

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

AEs should be collected using questionnaires and face-to-face interviews with the participant. The Adverse Effects Form is a targeted checklist-based questionnaire with items selected to detect common side effects from product use. This questionnaire also contains an open-ended section for participants to record any additional effects.

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

11.2.1 Period of Collection

All existing health conditions identified during the Screening Period will be recorded as concomitant disease and the participant's eligibility will be reviewed. Any AEs which occur during the screening session will be captured by the study site staff and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study procedures.

Any new, clinically relevant, abnormal finding detected during the study or worsening of a pre-existing condition/concomitant disease will be documented as an AE or an SAE.

11.3 Assessment of Adverse Events

11.3.1 Intensity of Adverse Events

For each AE/SAE, the intensity will be graded on a 3-point intensity scale:

- Mild: The AE is easily tolerated and does not interfere with daily activity.
- Moderate: The AE interferes with daily activity, but the participant is still able to function.
- Severe: The AE is incapacitating and requires medical intervention.

11.3.2 Relationship to Study Procedures

In general, all AEs and SAEs will be assessed by the Investigator or designee as either 'related' or 'not related'.

- Not related: The temporal relationship of the clinical event to study procedures and/or the study medication makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Related: The temporal relationship of the clinical event to study procedures and/or the study medication makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

11.4 Follow-up of Non-serious and Serious Adverse Events

Non-serious AEs will not be followed-up by the Investigator or designee after the end of study. The Investigator or designee will refer the participant to their Primary Care Provider for follow up of those AE(s) until they have resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found.

Serious AEs will be followed up by the Investigator or designee, despite their continuation after the end of study, until their resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g. a chronic condition).

11.5 Reporting of Safety Events to IRB

The Principal Investigator will report all serious adverse events relating to the study in an expedited manner to the Institutional Review Board (IRB) office in accordance with the Center's standard operating procedures and GCP reporting guidelines.

11.6 Reporting of Safety Events to FDA

The Principal Investigator will report any suspected adverse reaction to study treatment that is both serious and unexpected to the FDA following established Safety Reporting guidelines.

11.7 Reporting and Follow-Up of Pregnancies

All participants who are determined to be pregnant after enrollment will be discontinued from the study. Advice on the risk of smoking and smoking cessation will be provided by the study doctor (or qualified staff) and participants will be referred to the respective health care facility/health care provider for further support.

The Investigator is responsible for informing the IRB of any pregnancy that occurs during the study, and its outcome, according to local regulations.

11.8 Adverse Event Leading to Discontinuation

If a participant is discontinued from the study because of an AE, the Investigator or designee will follow up until the AE(s) has/have been resolved, stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found.

12 Data Management

12.1 Data Collection Procedures

Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. Any corrections made to source documents

must be clearly recorded, without obscuring the original values and be accompanied by the date of change and identification of the person making the change.

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

12.2 Protocol Deviations / Noncompliance

Protocol deviations are defined as deviations from the study procedures as defined in this document, whether intentional or unintentional that may affect the participant's rights, safety, or well-being and/or the completeness, accuracy and reliability of the data.

Noncompliance that meets the above definition must be reported to the IRB within 10 days of becoming aware of the noncompliance.

12.3 Data Capture

All data are collected from participants using paper documents or an electronic data capture system. All applicable data, as specified in the protocol, will be transferred to the database or applicable Case Report Forms.

12.3.1 Salesforce.com

Data will be collected for recruitment and screening purposes as stated within an Advarra IRB generic recruitment protocol. Unrelated to that protocol, pre-screening questionnaires will be attached to potential participant's records on whether they qualify or are disqualified for this study. Questionnaires utilized for this study will be permanently attached to that potential volunteer's record unless that information is requested to be removed by the participant.

12.3.2 Survey Monkey

Survey Monkey uses some of the most advanced technology for Internet security that is commercially available today. This Security Statement is aimed at being transparent about our security infrastructure and practices, to help reassure that data is appropriately protected. Visit Survey Monkey privacy policy for more information on data handling.

All Survey Monkey information systems and infrastructure are hosted in world-class data centers. These data centers include all the necessary physical security controls you would expect in a data center these days (e.g., 24×7 monitoring, cameras, visitor logs, entry requirements). SurveyMonkey has dedicated cages to separate our equipment from other tenants. In addition, these data centers are SOC 2 accredited.

12.3.3 Short Message Service (SMS) Messaging

SMS Messaging will be utilized for the delivery of a hyperlink to a mobile device to collect study data. This data will be collected utilizing an electronic survey. The service utilized for these messages is textit.in.

12.3.4 Medrio

All smoking behavioral and self-report measures will be captured initially using Medrio. Medrio is an electronic data collection system that records and performs analysis and reporting of data. Participant data will be kept within Medrio's secure servers and may only be transmitted through a secure (SSL) download to our local server. Medrio's servers are protected by high-end firewall systems, with vulnerability scans performed regularly. All services have quick failover points with redundant hardware, and complete encrypted backups are performed regularly. Medrio uses Transport Layer Security (TLS) encryption (SSL or HTTPS) for all transmitted internet data. All information collected within Medrio is compliant with 21 CFR 11 requirements.

12.4 Missing Data

Missing data will remain as missing, i.e., no attempt will be made to impute missing values and only observed values will be used in data summarizations and analysis.

12.5 Data Handling

Data of all participants enrolled including screening failures and AE/SAEs during the study (from the time of informed consent to the end of the study of the participant) will be captured in the source documents.

12.6 Data Validation

Data that are entered will be verified and edit checked to ensure accuracy. Inconsistencies that arise from these checks will be resolved and documented by study staff.

12.7 Database Lock

Upon completion of the trial, after data entry is complete, the data has been cleaned, and the principal investigator has reviewed and provided approval, the database will be locked, and final write access will be removed.

13 Planned Statistical Methods

All data measures (e.g., withdrawal symptoms questionnaires, smoking history, smoking diaries, etc.) are captured initially using paper or an electronic data capture system. Verified data files will be analyzed using Statview or SAS (Statview, SAS Institute, Cary NC). Data will be inspected for outliers and if sufficiently extreme (Chauvenet's criterion, after verifying normality of distributions) will be censored from the data analysis.

13.1 Efficacy and Tolerability

13.1.1 Abstinence Outcomes

Abstinence at each time point will be defined by a self-report of no cigarette smoking (not even a puff) since the prior session, confirmed by an expired air CO reading of less than 5 ppm. The primary

abstinence outcome will be abstinence during weeks 8-11 post-quit date. An intent-to-treat approach will be taken in which any participants lost to follow-up after the point of randomization, or who have relapsed prior to the end of treatment (week 11 post-quit) will be counted as non-abstinent (in accordance with recent guidelines from the FDA). A secondary smoking abstinence outcome will be 7-day point abstinence at 6 months post-quit, for participants who have not relapsed prior to the end of treatment. The main goal of the 6-month follow-up is to assess the persistence of therapeutic effects for those who do achieve end-of-treatment abstinence. This information will be helpful in determining the treatment duration in future Phase 3 clinical trials. The main hypothesis to be evaluated in this pilot study is that the incidence of varenicline-associated side effects, specifically nausea, will be diminished by co-administration of hydroxyzine, relative to historical benchmarks (see below). A one-tailed test of abstinence will be conducted, however, comparing the proportion of participants abstinent during weeks 8-11 to the historical benchmark of 45% abstinence, to provide evidence that abstinence is not significantly lower than it would be with varenicline alone. There is no reason to expect that abstinence rate would be reduced by hydroxyzine; if anything, abstinence would be expected to be enhanced by amelioration of varenicline-associated side effects and by potential effects of H1 antagonists to reduce nicotine reward.[35]

13.1.2 Side Effects / Tolerability

The hypothesis that hydroxyzine reduces the incidence of nausea, one of the most common side effects of varenicline, will be evaluated by comparison to the benchmark of 30% (20% above placebo rate of 10%) observed in clinical trials of varenicline.[36] Initially, 25 participants will be recruited and then the possibility of recruiting 25 more (total N=50) depending on an interim analysis, as follows:

- If 0-3 participants out of 25 (12% or less) report nausea, we would conclude the treatment is highly promising at the interim stage and go directly to an RCT (Branch 1).
- If 4-6 participants (out of 25) report the side effect, then the treatment will be deemed sufficiently promising to recruit an additional 25 participants (Branch 2). If 10 or less of the total 50 report the side effect of nausea (20% or less), a follow-up RCT would be warranted; otherwise the treatment would be deemed unpromising.
- If 7 or more out of 25 (28% or more) report the side effect of nausea in the interim analysis, then we would conclude it is futile to continue the pilot and the study would be terminated (Branch 3).

The frequency of treatment-emergent side effects (i.e., those that begin or worsen after the initiation of treatment) will be tabulated. Due to the problem of Type II error posed by significance testing numerous side effect outcomes (especially if corrections are imposed for multiple comparisons), descriptive statistical methods will instead be used, supplemented by calculation of confidence intervals and p-values as a flagging device to highlight differences worthy of further attention.[37] Hypothesis testing will be conducted for only two outcomes: 1) proportion of participants that withdraw from the study due to side effects; 2) overall adherence (i.e., proportion of scheduled doses taken) assessed by daily medication diaries and returned capsules.

13.1.3 Statistical Power

Monte Carlo simulations conducted by our statistical consultant (Dr. Dan Bauer) revealed that if the combination hydroxyzine/varenicline treatment is no better than varenicline alone (null of 30% incidence of nausea is true) the following would occur:

- 3% go into Branch 1 (highly promising)
- 31% go into Branch 2 (larger pilot)

- 66% go into Branch 3 (early evidence of futility)
- Overall Type I error rate of 9%

If the new treatment yields a side effect rate of 15% (versus null of 30%) then:

- 47% go into Branch 1 (highly promising)
- 46% go into Branch 2 (larger pilot)
- 7% go into Branch 3 (futile)
- Overall power of 86%

If the new treatment yields a side effect rate no worse than placebo of 10% (versus null of 30%) then:

- 77% go into Branch 1 (highly promising)
- 22% go into Branch 2 (larger pilot)
- 1% go into Branch 3 (futile)
- Overall power of 98%

Thus, to detect a clinically important reduction in side effects (a relative reduction by at least 50%, from an incidence of 30% to 15% or less), the power exceeds 86%. The Type I error of the overall approach is 9%.

13.2 Interim Analysis

An interim analysis will be conducted after results are collected from the first 25 participants, in order to determine whether the trial will stop, or an additional 25 participants will be enrolled, as described above.

14 Ethics and Regulations

14.1 IRB Approval

The protocol, informed consent document and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB prior to being used.

Any change to the protocol must be submitted to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately provided the reviewing IRB are notified within 10 working days.

14.2 Investigational New Drug Application

An Investigational New Drug (IND) application is not required for either medication since both medications have been approved by the FDA for the intended purposes. Since varenicline and hydroxyzine are FDA-approved medications, marketed in the United States, they do not require an IND. This study is not intended to support a new indication, support a change in labeling, support a change in advertising, nor does it involve a change in dosage level or route of administration.

14.3 GCP and Regulatory Requirements

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

14.4 Participant Information and Consent

It is the responsibility of the investigator to provide each participant with full and adequate verbal and written information using the IRB-approved informed consent form (ICF), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures.

The signed and personally dated original and completed ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the participant's files and a copy must be given to the participant. The participant will be informed that if they discontinue from the study, the data collected until the point of discontinuation will be maintained as part of the study data and the samples collected prior to discontinuation will be analyzed, unless they refuse in writing.

14.5 Amendment to Informed Consent Form

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will ensure that the documents have been reviewed and approved by the IRB before participants are informed and sign the amended ICF (including date and time).

15 Administrative Considerations

15.1 Participant Confidentiality

All information obtained during the conduct of the study with respect to the participants' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the participant. An agreement to disclose any such information will be obtained from the participant in writing and signed by the participant, in compliance with all local and national data protection and privacy legislation.

Study records that identify participants will be kept confidential as required by law. Except when required by law, participants will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Rose Research Center. For records disclosed outside of Rose Research Center, participants will be assigned a unique code number. The key to the code will be kept separate from the locked file where the study records are stored.

15.2 Record Retention

All records of data, in any form, will be maintained by Rose Research Center as required by ICH/GCPs. Essential documents will be retained for at least 15 years after completion of the study.

Appropriate measures will be taken to prevent accidental or premature destruction of these documents.

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Appendix 1 – Perceived Stress Scale 10-Item (PSS-10)

Perceived Stress Scale (10-Item)

Please answer the following questions:

	Never	Almost Never	Sometimes	Fairly Often	Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	❍	❍	❍	❍	❍
2. In the last month, how often have you felt that you were unable to control the important things in your life?	❍	❍	❍	❍	❍
3. In the last month, how often have you felt nervous and "stressed"?	❍	❍	❍	❍	❍
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	❍	❍	❍	❍	❍
5. In the last month, how often have you felt that things were going your way?	❍	❍	❍	❍	❍
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	❍	❍	❍	❍	❍
7. In the last month, how often have you been able to control irritations in your life?	❍	❍	❍	❍	❍
8. In the last month, how often have you felt that you were on top of things?	❍	❍	❍	❍	❍
9. In the last month, how often have you been angered because of things that were outside of your control?	❍	❍	❍	❍	❍
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	❍	❍	❍	❍	❍

Appendix 2 – State-Trait Anxiety Inventory 6-Item (STAI)

6-Item State-Trait Anxiety Inventory (STAI)

Please answer the following questions:

	Not at all	Somewhat	Moderately	Very much
1. I feel calm.	❍	❍	❍	❍
2. I feel tense.	❍	❍	❍	❍
3. I feel upset.	❍	❍	❍	❍
4. I am relaxed.	❍	❍	❍	❍
5. I feel content.	❍	❍	❍	❍
6. I am worried.	❍	❍	❍	❍

Appendix 3 - Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	❍	❍	❍	❍
2. Feeling down, depressed, or hopeless	❍	❍	❍	❍
3. Trouble falling or staying asleep, or sleeping too much	❍	❍	❍	❍
4. Feeling tired or having little energy	❍	❍	❍	❍
5. Poor appetite or overeating	❍	❍	❍	❍
6. Feeling bad about yourself- or that you are a failure or have let yourself or your family down	❍	❍	❍	❍
7. Trouble concentrating on things, such as reading the newspaper or watching television	❍	❍	❍	❍
8. Moving or speaking so slowly that other people could have noticed. Or the opposite- being so fidgety or restless that you have been moving around a lot more than usual	❍	❍	❍	❍
9. Thoughts that you would be better off dead, or of hurting yourself in some way	❍	❍	❍	❍

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- ❍ Not difficult at all
- ❍ Somewhat difficult
- ❍ Very difficult
- ❍ Extremely difficult

Appendix 4 – Minnesota Nicotine Withdrawal Scale Revised (MNSW-R)

MINNESOTA NICOTINE WITHDRAWAL SCALE REVISED (MNWS-R)

INSTRUCTIONS: Please rate yourself based on the last 24 hours.

	None	Slight	Mild	Moderate	Severe
1. Angry, irritable, frustrated	❍	❍	❍	❍	❍
2. Anxious, nervous	❍	❍	❍	❍	❍
3. Depressed mood, sad	❍	❍	❍	❍	❍
4. Desire or craving to smoke	❍	❍	❍	❍	❍
5. Difficulty concentrating	❍	❍	❍	❍	❍
6. Increased appetite, hungry, weight gain	❍	❍	❍	❍	❍
7. Insomnia, sleep problems, awakening at night	❍	❍	❍	❍	❍
8. Restless	❍	❍	❍	❍	❍
9. Impatient	❍	❍	❍	❍	❍
10. Constipation	❍	❍	❍	❍	❍
11. Dizziness	❍	❍	❍	❍	❍
12. Coughing	❍	❍	❍	❍	❍
13. Dreaming or nightmares	❍	❍	❍	❍	❍
14. Nausea	❍	❍	❍	❍	❍
15. Sore throat	❍	❍	❍	❍	❍

Appendix 5 – Fagerström Test for Nicotine Dependence (FTND)

FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

INSTRUCTIONS: Please mark the answer that most accurately answers each question.

1. How soon after you wake up do you smoke your first cigarette?

   ❍ Within 5 Minutes ❍ 6-30 Minutes ❍ 31-60 Minutes ❍ After 60 Minutes

2. Did you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in the cinema, etc.?

   ❍ Yes
   ❍ No

3. Which cigarette would you hate most to give up?

   ❍ The first one in the morning
   ❍ Any other

4. How many cigarettes per day do you smoke?

   ❍ 31 or more ❍ 21-30 ❍ 11-20 ❍ 10 or less

5. Do you smoke more frequently during the first hours of waking than during the rest of the day?

   ❍ Yes
   ❍ No

6. Do you smoke if you are so ill that you were in bed most of the day?

   ❍ Yes
   ❍ No

Appendix 6 – The Wisconsin Predicting Patients' Relapse Questionnaire (WI-PREPARE)

WI-PREPARE QUESTIONNAIRE

Please answer the questions below using the responses listed.

1. If someone in your household wants to smoke, does he/she have to leave in order to smoke?
   - ❑ Yes
   - ❑ No
2. Which of these statements best describes your place of work's smoking policy for work areas?
   - ❑ Smoking is not allowed in any work areas
   - ❑ Smoking is allowed in some work areas
   - ❑ Smoking is allowed in all work areas
   - ❑ N/A, I do not work outside the home

		Not at all true 1	2	3	4	5	6	Extremely true of me 7
3.	I'm around smokers much of the time.							
4.	When I haven't been able to smoke for a few hours, the craving gets intolerable.							

5. How soon after you wake up do you smoke?
   - ❑ After 60 minutes
   - ❑ 31 – 60 minutes
   - ❑ 6 – 30 minutes
   - ❑ Within 5 minutes
6. How many cigarettes a day do you smoke?
   - ❑ 10 or less
   - ❑ 11 - 20
   - ❑ 21 - 30
   - ❑ 31 or more
7. What is the highest grade or year of school that you completed?
   - ❑ Never attended, or only attended kindergarten
   - ❑ Grades 1 – 8 (elementary)
   - ❑ Grade 9 – 11 (some high school)
   - ❑ Grade 12 or GED (high school graduate)
   - ❑ College 1 to 3 years (some college or technical school
   - ❑ College 4 years or more (4-year college graduate)

Appendix 7 - Research Participant Payment Verification Form

RESEARCH PARTICIPANT PAYMENT VERIFICATION FORM

Receipt for Payment:

In order for Rose Research Center to meet its obligations to the Internal Revenue Service we are required to obtain the following information. Payment received as compensation for participation in research is considered taxable income. You are responsible for paying any state, federal or Social Security taxes on the money you receive. If your total payment exceeds $600 in any one calendar year, we are required to report this information to the Internal Revenue Service (IRS).

The Payment Verification Form will be used in order to process your payments only. Once your information has been entered into the Greenphire payment system, this form will be destroyed. Until that time, the form will be kept in a secure and locked area at all times. Your information will not be connected to your responses to the interviews, surveys, questionnaires or with your participation in this study.

Full Name: _____

Social Security Number: _____

Permanent Home Address:

_____

_____

_____

Appendix 8 – Smoking History

SMOKING HISTORY

What brand of cigarettes do you smoke? _____

Color of cigarette pack? _____

Size: ❍ Kings ❍ Regulars ❍ 72's ❍ 100's ❍ 120's

Flavor: ❍ Menthol ❍ Non-menthol

Pack type: ❍ Hard pack ❍ Soft pack

Filtered? ❍ Filtered ❍ Unfiltered

1. How many cigarettes do you smoke a day? _____cigs per day

2. How old were you when you first smoked a cigarette? _____ years old

3. How old were you when you became a regular smoker? _____ years old

4. How many years have you been a regular smoker? _____ years

5. How many times have you tried to seriously quit smoking (for at least 1 day)? _____ attempts

6. Since you first started smoking, what was the longest period of time that you were able to stay off cigarettes? (If less than 1 day, do not include time sleeping) _____
❍ Hours ❍ Days ❍ Weeks ❍ Months ❍ Years

7. Have you been a regular for the past 12 months?
❍ Yes ❍ No

8. Do you have the desire to quit smoking in the next 30 days?
❍ Yes ❍ No

9. Did your mother smoke cigarettes while pregnant with you?
❍ Yes ❍ No ❍ I don't know

10. Does someone you live with smoke cigarettes?
❍ Yes ❍ No

11. Have you smoked cigar in the past 14 days?
❍ Yes ❍ No

12. Have you smoked a pipe, hookah or an e-cigarette in the past 14 days?
❍ Yes ❍ No

13. Have you used snuff or chewing tobacco in the past 14 days?
❍ Yes ❍ No

14. Do you wake in the middle of the night to smoke?
❍ Yes ❍ No

Appendix 9 – Registration Form

REGISTRATION FORM

(Please Print)

Today's Date:			Participant Number:	
CONTACT INFORMATION				
Last Name:	First:	Middle Initial:	❑ Mr. ❑ Mrs.	❑ Miss ❑ Ms.
Street Address:				
P.O. Box:	City:	State:	ZIP Code:	
E-mail Address:			Do you have web access other than your mobile phone? ❑ Yes ❑ No	
Primary Phone Number: ( )	Cell Office Home	Other Phone Number: ( )	Cell Office Home	
Do you give Rose Research Center permission to leave a message at the above numbers?			❑ Yes	❑ No
Emergency contact: If I cannot be reached or if there is an emergency you can leave a message with:				
Name of local friend or relative:		Relationship:	Phone no.: ( )	
_____ I understand in the event that I do not return messages and fail to come to appointments my emergency contact person may be contacted.				

DEMOGRAPHIC INFORMATION			
Birth Date: / /	Sex: ❑ M ❑ F	Marital Status (circle one):	Single / Married / Divorced / Separated / Widowed
Race: ❑ American Indian or Alaska Native ❑ Asian ❑ Black or African American ❑ Native Hawaiian or Other Pacific Islander ❑ White ❑ Other (specify) _____		Ethnicity: ❑ Hispanic or Latino ❑ Not Hispanic or Latino	
Are you a U.S. Veteran?		❑ Yes	❑No
Are you currently employed at or have affiliation with the Rose Research Center?		❑ Yes	❑No
Are you currently participating in another clinical trial?		❑ Yes	❑No
Have you participated in a clinical trial in the past 3 months that included an investigational drug?		❑ Yes	❑No

I attest that all of the information above is to the best of my knowledge and believe true, correct and complete.

_____ _____

Participant's Signature Date

IDENTIFICATION VERIFICATION

(Office use only)

Form of ID Verified: ❑ Driver's License ❑ Photo ID ❑ Military ID ❑ Passport

_____ _____

Research Personnel's Signature Date

Appendix 10 – Medical History Form

MEDICAL HISTORY FORM

Major Medical Conditions

Have you ever had or are currently having/ being treated for any of the following conditions?

❑ Yes	❑ No	High blood pressure (Hypertension)
❑ Yes	❑ No	Heart attack, Heart Failure, OR heart disease diagnosis by cardiac angiogram
❑ Yes	❑ No	Problems with heart valves such as mitral regurgitation, stenosis, artificial valve or other
❑ Yes	❑ No	Heart rhythm problem such as atrial fibrillation, tachycardia, or pacemaker
❑ Yes	❑ No	Prior surgery on the gastrointestinal tract (e.g. colectomy, gastric by-pass, Reux-En-Y)
❑ Yes	❑ No	Skin problems
❑ Yes	❑ No	Cirrhosis of the liver
❑ Yes	❑ No	Liver problems other than cirrhosis (e.g. Hepatitis, fatty liver)
❑ Yes	❑ No	Kidney failure
❑ Yes	❑ No	Chronic Kidney Disease
❑ Yes	❑ No	Chronic Diarrhea and/or constipation such as Irritable Bowel Syndrome, Crohn's Disease, Inflammatory Bowel
❑ Yes	❑ No	Stomach/ Duodenal Ulcer (Gastrointestinal Ulcer)
❑ Yes	❑ No	Chronic Bronchitis (cough every morning)
❑ Yes	❑ No	Chronic Obstructive Pulmonary Disease (COPD) or Emphysema
❑ Yes	❑ No	Other lung disorder such as Tuberculosis, Pulmonary Fibrosis, Sarcoid
❑ Yes	❑ No	Asthma
❑ Yes	❑ No	Stroke or TIA (mini-stroke)
❑ Yes	❑ No	Seizure/ epilepsy
❑ Yes	❑ No	Migraine headaches
❑ Yes	❑ No	Unexplained fainting spells
❑ Yes	❑ No	Insomnia
❑ Yes	❑ No	Other neurologic conditions
❑ Yes	❑ No	Problems giving blood samples
❑ Yes	❑ No	Anemia requiring iron
❑ Yes	❑ No	Blood disorder
❑ Yes	❑ No	Rheumatic Disease such as Rheumatoid Arthritis, Fibromyalgia, other
❑ Yes	❑ No	Sinusitis/ Seasonal allergies
❑ Yes	❑ No	Other severe allergies
❑ Yes	❑ No	Diabetes or Pre-diabetes
❑ Yes	❑ No	Thyroid disease or condition
❑ Yes	❑ No	Cancer
❑ Yes	❑ No	Depression/ Anxiety/ Bipolar disorder
❑ Yes	❑ No	Post-traumatic stress disorder
❑ Yes	❑ No	Other Psychiatric problems (e.g., Borderline, Schizoaffective, Schizophrenia, Hypomania, AHDA)
❑ Yes	❑ No	History of Sexually Transmitted Disease (STD)
❑ Yes	❑ No	Chronic infectious syndrome such as HIV, CMV, Epstein Barr
❑ Yes	❑ No	History of drug or alcohol abuse
❑ Yes	❑ No	Intolerance to medications
❑ Yes	❑ No	Other major medical condition

Office use only:

Page 1 of 5

MEDICAL HISTORY FORM

Past Medical History

Please list any illnesses that have caused you to miss work or have interrupted your life this past year:

1.		Mo/Yr:	
2.		Mo/Yr:	
3.		Mo/Yr:	
4.		Mo/Yr:	
5.		Mo/Yr:	

Please list any hospitalizations. If possible, include the year:

1.		Mo/Yr:	
2.		Mo/Yr:	
3.		Mo/Yr:	
4.		Mo/Yr:	
5.		Mo/Yr:	

Please list any serious injuries or accidents. If possible, include the year:

1.		Mo/Yr:	
2.		Mo/Yr:	
3.		Mo/Yr:	
4.		Mo/Yr:	
5.		Mo/Yr:	

Please list any surgeries or major procedures, along with the reason. If possible, include the year:

1.		Mo/Yr:	
2.		Mo/Yr:	
3.		Mo/Yr:	
4.		Mo/Yr:	
5.		Mo/Yr:	

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MEDICAL HISTORY FORM

Family History

Has any first degree family members (children, parents, or siblings) had any of the following illnesses:

Illness	Which family member?
Anemia or Blood disease	
Cancer	
Diabetes	
Glaucoma	
Heart disease	
High blood pressure	
Mental Illness/ Depression/ Generalized Anxiety	
Stroke	
Substance abuse (alcohol, tobacco or other)	
Other serious illness:	

Social History

Please complete the following questions:

Do you drink alcohol, beer, or wine?	❑ Yes	❑ No	If YES, how many drinks per week? _____ How many drink do you have on your heaviest drinking day of the week? _____
Do you drink coffee, tea, caffeinated soda daily?	❑ Yes	❑ No	If YES, how many cups per day? _____
Have you used a non-prescription drug such as marijuana, cocaine, heroin in the last month? Have you used prescription drugs not prescribed to you?	❑ Yes	❑ No	If YES, when and what drug/ substance and last date of use: _____

Blood Donation

Please complete the following question:

Have you received or donated blood or blood products within the last 2 months?	❑ Yes	❑ No	If YES, when and which blood product (whole blood, plasma, platelets, etc.)? _____

General Health

Please complete the following questions:

Do you use supplemental oxygen?	❑ No	❑ Yes		
Can you walk up 2 flights of stairs?	❑ No	❑ Yes, without stopping	❑ Yes, but I need to stop along the way	
How well do you walk?	❑ Independently	❑ I use a cane or walker	❑ I use a wheelchair	
Do you use CPAP machine?	❑ No	❑ Yes		

MEDICAL HISTORY FORM

General Health (Women Only)

Do you agree to use a medically acceptable form of birth control for the duration of the study? ❑ N/A ❑ Yes ❑ No

If yes, please select form of contraception you plan to use or are currently using.

❑ Tubal ligation / Hysterectomy / Bilateral oophorectomy	❑ Spouse with vasectomy
❑ Birth control pills / patches / implants / injections	❑ Not heterosexually active
❑ Condom / Diaphragm used with spermicide	❑ None
❑ Intrauterine device (IUD) / Essure	

Do you plan to become pregnant in the next 6 months? ❑ Yes ❑ No

Medications

Please list any allergies (and the reaction caused by the allergy (e.g. "rash" or "tongue swelling" or "itchness"):

Please list all medications you have used within the last month (include over-the counter drugs, vitamins/ supplements, and especially prescriptions):

Name of medication	**Dosing** (mg. and times per day) and **Route** (oral, topical)	Start date	Stop date	Prescribed for what problem?

MEDICAL HISTORY FORM

Smoking Cessation Products

For each of the following, mark if you have used the product, experienced any side effects, allergy or intolerance with usage or had to stop using the product due to side effects:

	Not Used	Used	Side Effects	Stopped due to Side Effects	
Nicotine Patch	❑	❑		❑ Yes	❑ No
Nicotine Gum	❑	❑		❑ Yes	❑ No
Nicotine Lozenge	❑	❑		❑ Yes	❑ No
Nicotine Inhaler	❑	❑		❑ Yes	❑ No
Nicotine Nasal Spray	❑	❑		❑ Yes	❑ No
Zyban (wellbutrin)	❑	❑		❑ Yes	❑ No
Chantix (varenicline)	❑	❑		❑ Yes	❑ No

Have you used any of these products within the past 14 days? ❑ Yes ❑ No

MD/ PA Signature

Date

Appendix 11- Review of Systems Form

REVIEW OF SYSTEMS

Are you currently (in the last 30 days) having/ being treated for any of the following conditions:

General: *(____ none of these apply)*
- ❑ Unexplained weight loss or gain
- ❑ Fever or chills
- ❑ Trouble Sleeping
- ❑ Fatigue/ Lack of energy
- ❑ Weakness

Skin: *(____ none of these apply)*
- ❑ Rashes
- ❑ Itching
- ❑ Color changes
- ❑ Lumps
- ❑ Dryness
- ❑ Hair and nail changes

Head: *(____ none of these apply)*
- ❑ Headache
- ❑ Head Injury

Ears: *(____ none of these apply)*
- ❑ Decreased hearing
- ❑ Earache
- ❑ Ringing in ears

Eyes: *(____ none of these apply)*
- ❑ Vision problems
- ❑ Blurry or double vision
- ❑ Redness
- ❑ Specks
- ❑ Flashing lights
- ❑ Pain

Nose: *(____ none of these apply)*
- ❑ Stuffiness
- ❑ Itching
- ❑ Nose Bleeds
- ❑ Discharge
- ❑ Sinus pain

Throat: *(____ none of these apply)*
- ❑ Teeth/gum problems
- ❑ Sore tongue
- ❑ Thrush
- ❑ Dentures
- ❑ Dry mouth
- ❑ Non-healing sores
- ❑ Hoarseness
- ❑ Sore throat
- ❑ Difficulty swallowing

Neck: *(____ none of these apply)*
- ❑ Lumps
- ❑ Pain
- ❑ Swollen glands
- ❑ Stiffness

Respiratory: *(____ none of these apply)*
- ❑ Cough (dry or wet, productive)
- ❑ Coughing up blood
- ❑ Wheezing
- ❑ Shortness of breath
- ❑ Painful breathing

Cardiovascular: *(____ none of these apply)*
- ❑ Chest pain or discomfort
- ❑ Difficulty breathing lying down
- ❑ Suddenly awaking from sleep with shortness of breath
- ❑ Tightness
- ❑ Swelling
- ❑ Heart pounding/ Fluttering/ Palpitations
- ❑ Shortness of breath with activity

Gastrointestinal: *(____ none of these apply)*
- ❑ Swallowing difficulties
- ❑ Change in bowel habits
- ❑ Yellow eyes or skin
- ❑ Heartburn
- ❑ Rectal bleeding
- ❑ Change in appetite
- ❑ Constipation
- ❑ Diarrhea
- ❑ Nausea
- ❑ Vomiting
- ❑ Stomach pain

Urinary: *(____ none of these apply)*
- ❑ Frequency
- ❑ Blood in urine
- ❑ Change in urinary strength
- ❑ Urgency
- ❑ Pain with urination
- ❑ Incontinence

REVIEW OF SYSTEMS

Vascular: *(____ none of these apply)*
- ❑ Calf pain with walking
- ❑ Leg cramping
- ❑ Leg pains

Musculoskeletal: *(____ none of these apply)*
- ❑ Muscle or joint pain
- ❑ Back pain
- ❑ Swelling of joints
- ❑ Stiffness
- ❑ Redness of joints
- ❑ Trauma

Neurologic: *(____ none of these apply)*
- ❑ Dizziness
- ❑ Weakness
- ❑ Tremor
- ❑ Fainting
- ❑ Numbness
- ❑ Shaking episodes
- ❑ Tingling

Hematologic: *(____ none of these apply)*
- ❑ Bruise easily
- ❑ Bleed easily

Endocrine: *(____ none of these apply)*
- ❑ Heat or cold intolerance
- ❑ Frequent urination
- ❑ Change in appetite
- ❑ Sweating
- ❑ Thirst

Psychiatric: *(____ none of these apply)*
- ❑ Nervousness
- ❑ Memory loss
- ❑ Feeling down

Females only: *(____ none of these apply)*
- ❑ Pregnant or currently breast feeding

Office use only:

Appendix 12 – Employment History

EMPLOYMENT HISTORY

1. What is the highest degree you have completed?

- ❍ High school diploma or G.E.D.
- ❍ Technical degree
- ❍ Two year associates degree (e.g. A.A.)
- ❍ Four year undergraduate degree (e.g. B.A., B.S.)
- ❍ Professional degree (e.g. P.A., R.N.)
- ❍ Master's degree (e.g. M.A., M.S., M.B.A.)
- ❍ Doctorate (e.g. Ph. D., M.D., J.D.)
- ❍ Other_____

2. How many years of formal education have you completed: (Include grade school and higher) _____

3. What is your current employment status?

- ❍ Not employed (please answer question 4)
- ❍ Part-Time work
- ❍ Full-time work

4. If not employed is selected, please specify your answer:

- ❍ Education (Full-time student)
- ❍ Retired
- ❍ Medical leave
- ❍ Homemaker
- ❍ Laid off
- ❍ Other _____

5. What is your current job title; if no longer employed, in what position were you last employed?

_____

6. How physically demanding is your current employment?

- ❍ Not employed
- ❍ Not demanding at all
- ❍ Very little demanding
- ❍ A little demanding
- ❍ Somewhat demanding
- ❍ Moderately demanding
- ❍ Very demanding
- ❍ Extremely demanding

EMPLOYMENT HISTORY

7. How mentally or emotionally stressful is your current employment?

- ❍ Not employed
- ❍ Not stressful at all
- ❍ Very little stress
- ❍ A little stressful
- ❍ Somewhat stressful
- ❍ Moderately stressful
- ❍ Very stressful
- ❍ Extremely stressful

8. What is your gross (before taxes) annual household income?

- ❍ < $16,000
- ❍ $16,001- $32,000
- ❍ $32,001- $48,000
- ❍ $48,001- $64,000
- ❍ $64,001- $80,000
- ❍ $80,001- $96,000
- ❍ >$96,000

9. What are your estimated total assets? (Include house, automobiles, stocks, savings, furniture, etc.).

- ❍ <$50,000
- ❍ $50,001- $100,000
- ❍ $100,001- $200,000
- ❍ $200,001- $300,000
- ❍ $300,001- $400,000
- ❍ $400,001- $500,000
- ❍ $500,001- $750,000
- ❍ >$750,001

10. How many people live in your household? _____

Appendix 13 – Adverse Effects Form

ADVERSE EFFECTS FORM

Are you currently experiencing, or have you experienced any of the following since your previous visit?

INTENSITY RATINGS:
Mild – Easily tolerated and did not interfere with daily activity
Moderate – Interfered with daily activity, but you were still able to function
Severe – Incapacitated and required medical intervention

FREQUENCY RATINGS:
Rarely – Just once
Occasionally – A few times
Frequent – Several times / most of the time
Very Frequent – Everyday / constantly

Adverse Effect	N/A	Mild	Moderate	Severe	Rarely	Occasionally	Frequent	Very Frequent
Headache	❑	❑	❑	❑	❑	❑	❑	❑
Drowsiness (feel sleepy)	❑	❑	❑	❑	❑	❑	❑	❑
Fatigue	❑	❑	❑	❑	❑	❑	❑	❑
Nausea	❑	❑	❑	❑	❑	❑	❑	❑
Vomiting	❑	❑	❑	❑	❑	❑	❑	❑
Unusual heart rate	❑	❑	❑	❑	❑	❑	❑	❑

Are you experiencing (or have you experienced) any other effects not listed above?
If yes, please list one item on each row below and rate accordingly.

INTENSITY RATINGS:
Mild – Easily tolerated and did not interfere with daily activity
Moderate – Interfered with daily activity, but you were still able to function
Severe – Incapacitated and required medical intervention

FREQUENCY RATINGS:
Rarely – Just once
Occasionally – A few times
Frequent – Several times / most of the time
Very Frequent – Everyday / constantly

Adverse Effect	N/A	Mild	Moderate	Severe	Rarely	Occasionally	Frequent	Very Frequent
	❑	❑	❑	❑	❑	❑	❑	❑
	❑	❑	❑	❑	❑	❑	❑	❑
	❑	❑	❑	❑	❑	❑	❑	❑
	❑	❑	❑	❑	❑	❑	❑	❑
	❑	❑	❑	❑	❑	❑	❑	❑

MD/ PA Signature _____ Date _____

Appendix 14 – Daily SMS Survey

* 1. Hello {{ custom.fname }}
Please rate your experience with the following items in the past 24 hours

	None	Mild	Moderate	A Lot	Extreme
Stress	○	○	○	○	○
Difficulty sleeping	○	○	○	○	○
Nausea	○	○	○	○	○

* 2. Have you smoked any cigarettes today?

- ○ Yes
- ○ No

* 3. How soon after you woke up did you smoke your first cigarette?

- ○ Within 5 minutes
- ○ 6 to 30 minutes
- ○ 31 to 60 minutes
- ○ After 60 minutes

* 4. How many cigarettes did you smoke today?

* 5. Did you take your study drugs this morning?

- ○ Yes
- ○ No

* 6. Did you take your study drugs this evening?

- ○ Yes
- ○ No

Appendix 15 -Quit Assist Resource

QUITTING TAKES HARD WORK AND A LOT OF EFFORT, BUT—

You Can Quit Smoking

SUPPORT AND ADVICE FROM THE PUBLIC HEALTH SERVICE AND ROSE RESEARCH CENTER

WANT TO QUIT?

- Nicotine is a powerful addiction.
- Quitting is hard, but don't give up. **You can do it.**
- Many people try 2 or 3 times before they quit for good.
- Each time you try to quit, the more likely you will be to succeed.

GOOD REASONS FOR QUITTING:

- You will live longer and live healthier.
- The people you live with, especially your children, will be healthier.
- You will have more energy and breathe easier.
- You will lower your risk of heart attack, stroke, or cancer.

TIPS TO HELP YOU QUIT:

- Get rid of ALL cigarettes and ashtrays in your home, car, or workplace.
- Ask your family, friends, and coworkers for support.
- Stay in nonsmoking areas.
- Breathe in deeply when you feel the urge to smoke.
- Keep yourself busy.
- Reward yourself often.

QUIT AND SAVE YOURSELF MONEY:

- At over $5.00 per pack, if you smoke 1 pack per day, you will save more than $1,800 each year and more than $18,000 in 10 years.
- What else could you do with this money?

FROM: U.S. Department of Health and Human Services Public Health Service
ISSN 1530-6402
Revised September 2008
Modified for use by Rose Research Center May 2019

FIVE KEYS FOR QUITTING

1. GET READY.

- Set a quit date and stick to it—not even a single puff!
- Think about past quit attempts. What worked and what did not?

2. GET SUPPORT AND ENCOURAGEMENT.

- Tell your family, friends, and coworkers you are quitting.
- Tell your doctor or other health care provider that you are enrolled in this study.
- You can get free help by calling 1-800-QUIT NOW (784-8669) to be connected to the quitline in your State. **PLEASE CONTACT RRC STAFF BEFORE MAKING ANY CHANGES.**

3. LEARN NEW SKILLS AND BEHAVIORS.

- When you first try to quit, change your routine.
- Reduce stress.
- Distract yourself from urges to smoke.
- Plan something enjoyable to do every day.
- Drink a lot of water and other fluids.
- Replace smoking with low-calorie food such as carrots.

4. USE THE MEDICATION FROM THIS STUDY AND USE THEM CORRECTLY.

- Hydroxyzine (Vistaril).
- Varenicline (Chantix).
- Tell the RRC Staff if you want to use something different to help you quit smoking.
- **PLEASE CONTACT RRC STAFF BEFORE MAKING ANY CHANGES.**

5. BE PREPARED FOR RELAPSE OR DIFFICULT SITUATIONS.

- Avoid alcohol.
- Be careful around other smokers.
- Improve your mood in ways other than smoking.
- Eat a healthy diet and stay active.

Quitting smoking is hard. Be prepared for challenges, especially in the first few weeks.

Appendix 16 –SMS Observation Survey (after enrollment – prior to V2)

* 1. Hi {{ custom.fname }}
How soon after you woke up did you smoke your first cigarette?

- ◯ Within 5 minutes
- ◯ 6 to 30 minutes
- ◯ 31 to 60 minutes
- ◯ After 60 minutes

* 2. How many cigarettes did you smoke today?

* 3. Please rate your experience with the following items in the past 24 hours

	None	Mild	Moderate	A Lot	Extreme
Stress	◯	◯	◯	◯	◯
Difficulty sleeping	◯	◯	◯	◯	◯
Nausea	◯	◯	◯	◯	◯

Appendix 17 – Participant Instructions for Hydroxyzine

Rose Research Center, LLC Main Office • 7240 ACC Blvd. • Raleigh, NC 27617 • (919) 328-2345

INSTRUCTIONS FOR PROPER USE OF HYDROXYZINE (VISTARIL)

How does it work?

This medicine is normally prescribed to relieve itching, but it also can be prescribed to help insomnia (trouble sleeping), anxiety, nausea (feeling like throwing up), or treat an allergic reaction.

How do I take this medicine?

1. Take hydroxyzine exactly as directed. The blister packs are designed to help you take the medicine properly.
    a. For the first 3 days, take two tablets (25 mg tablets) at bedtime.
    b. After 3 days take one tablet (25 mg tablet) in the morning and two tablets (25 mg tablets) at bedtime.
    c. Only change your medicine at the direction of the study personnel or if you have a serious concern.
2. Do not crush, chew or split the tablet
3. Take hydroxyzine after eating and with a full glass (8 ounces) of water (do NOT drink alcohol with hydroxyzine).
4. We will schedule you to start taking hydroxyzine about 7 days before your actual quit date (the day you stop smoking).
5. If you forget to take a dose of hydroxyzine, take is as soon as you remember. If it is almost time for your next dose (less than 6 hours), just wait and take your next dose at the regular time. Do NOT take any extra tablets to make up for the dose(s) you forgot.
6. Keep this medication in a safe place, AWAY FROM CHILDREN. It should be stored at room temperature (not in your car) and away from direct sun, excessive heat, cold, or moisture. You MUST return any unused medication.

Precautions

Hydroxyzine should not be used by anyone who has problems with their heart. If you are concerned, please talk with the staff at Rose Research Center (919-328-2345). You may also call the 24-hour emergency advice line and speak with our study physician (855-999-1940) if you feel there is an emergency.

Use caution driving and operating machinery when you first start taking hydroxyzine until you know how it is going to affect you. Some people feel sleepy, dizzy, or have trouble concentrating when they first start hydroxyzine.

There is a risk of fainting caused by hydroxyzine. If you feel lightheaded, dizzy, or notice a really fast heart rate, and these symptoms persist for more than 5 minutes, then you should stop taking hydroxyzine and get medical attention right away. Inform the staff at Rose Research Center AFTER you obtain medical care.

You should tell the staff at Rose Research Center if you have any allergies to medicines, including hydroxyzine.

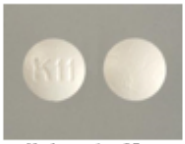
You should also inform the staff at Rose Research Center if you believe you may be pregnant (for women only).

Potential Side Effects

In some people, hydroxyzine can cause:

Dry mouth	Constipation (hard to poop)
Confusion (especially in older adults)	Headaches
Unintentional trembling or shaking movements	Upset stomach
Drowsiness (feeling REALLY sleepy)	Blurred vision

If you experience any of these side effects, or any other side effects, please notify the staff at Rose Research Center.



Hydroxyzine 25 mg

Appendix 18 – Participant Instructions for Varenicline

Rose Research Center, LLC Main Office • 7240 ACC Blvd. • Raleigh, NC 27617 • (919) 328-2345

INSTRUCTIONS FOR PROPER USE OF VARENICLINE (CHANTIX)

How does it work?

This medicine helps a person to stop smoking by reducing the desire (urge) to smoke.

How do I take this medicine?

1. Take varenicline exactly as directed. The blister packs are designed to help you take the medicine properly.
   a. For the first 3 days, take one tablet (0.5 mg) at bedtime.
   b. For days 4-7, take one tablet (0.5 mg) in the morning and one tablet (0.5 mg) at bedtime.
   c. For the rest of the time, take one tablet (1.0 mg) in the morning and one tablet (1.0 mg) at bedtime.
   d. Only change your medicine at the direction of the study personnel or if you have a serious concern.
2. Do not crush, chew or split the tablet
3. Take varenicline after eating and with a full glass (8 ounces) of water (do NOT drink alcohol with varenicline).
4. We will schedule you to start taking varenicline about 7 days before your actual quit date (the day you stop smoking).
5. If you forget to take a dose of varenicline, take is as soon as you remember. If it is almost time for your next dose (less than 6 hours), just wait and take your next dose at the regular time. Do NOT take an extra tablet to make up for the dose you forgot.
6. Keep this medication in a safe place, AWAY FROM CHILDREN. It should be stored at room temperature (not in your car) and away from direct sun, excessive heat, cold, or moisture. You MUST return any unused medication.

Precautions

Some people have reported changes in behavior, agitation, depression, thoughts of suicide, or hostility. If you experience any of these issues, please call Rose Research Center and speak with one of our helpful staff (919-328-2345). You may also call the 24-hour emergency advice line and speak with our study physician (855-999-1940) if you feel this is an emergency.

As with most any medication, there is a risk of having an allergic reaction to varenicline. This can be serious, especially if you experience swelling of the face, mouth, tongue, or throat which causes difficulty breathing. If you have any of these symptoms, stop taking varenicline and get medical attention right away. Inform the staff at Rose Research Center AFTER you obtain medical care for these symptoms.

You should tell the staff at Rose Research Center if you have any allergies to medicines, including varenicline.

You should also inform the staff at Rose Research Center if you believe you may be pregnant (for women only).

Use caution driving and operating machinery when you first start taking varenicline until you know how it is going to affect you. Some people feel sleepy, dizzy, or have trouble concentrating when they first start varenicline.

Potential Side Effects

In some people, varenicline can cause:

Nausea (feel like throwing up)	Insomnia (trouble sleeping)
Unusual dreams	Mood changes
Headaches	Constipation (hard to poop)
Gas	Vomiting

If you experience any of these side effects, or any other side effects, please notify the staff at Rose Research Center.

Varenicline 1.0 mg

Varenicline 0.5 mg

Appendix 19 – 6-Month Follow Up Survey

* 1. Hello {{ custom.fname }}
Did you smoke a cigarette since your last visit?

- ◯ Yes
- ◯ No

2. If yes, are you still smoking cigarettes right now?

- ◯ Yes
- ◯ No

Appendix 20 – Cigarette Evaluation Questionnaire modified (mCEQ)

CIGARETTE EVALUATION QUESTIONNAIRE - modified

Please answer the following questions_____

	Not at all	Very little	A little	Moderately	A lot	Quite a lot	Extremely
1. Was it satisfying?	❍	❍	❍	❍	❍	❍	❍
2. Did it taste good?	❍	❍	❍	❍	❍	❍	❍
3. Did it make you dizzy?	❍	❍	❍	❍	❍	❍	❍
4. Did it calm you down?	❍	❍	❍	❍	❍	❍	❍
5. Did it help you concentrate?	❍	❍	❍	❍	❍	❍	❍
6. Did it make you feel more awake?	❍	❍	❍	❍	❍	❍	❍
7. Did it reduce your hunger for food?	❍	❍	❍	❍	❍	❍	❍
8. Did it make you nauseated?	❍	❍	❍	❍	❍	❍	❍
9. Did it make you feel less irritable?	❍	❍	❍	❍	❍	❍	❍
10. Did you enjoy the sensations of the smoke in your throat and chest?	❍	❍	❍	❍	❍	❍	❍
11. Did it immediately reduce your craving for cigarettes?	❍	❍	❍	❍	❍	❍	❍
12. Did you enjoy smoking?	❍	❍	❍	❍	❍	❍	❍