Combination of E-cigarettes and Varenicline for Tobacco Harm Reduction

NCT04210180

Protocol V4.0 – 23 Mar 2020

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Clinical Study Protocol

Study Title:	Combination of E-cigarettes and Varenicline for Tobacco Harm Reduction
Sponsor:	Foundation for a Smoke-Free World
Version Number:	Version 4.0
Version Date:	March 23, 2020
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TABLE OF CONTENTS

APPENDIX

LIST OF ABBREVIATIONS

ABI	Ankle Brachial Index
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 explore the impact of varenicline on the process of switching from combustible cigarettes (CC) to an e-cigarette. Varenicline is currently the most efficacious single pharmacotherapy for smoking cessation, and through its actions as an agonist or partial agonist at various nicotinic acetylcholine receptor subtypes, serves to diminish the rewarding effects of cigarette smoking. Diminishing the rewarding effects of smoking might facilitate the transition from CC to e-cigarettes. On the other hand, varenicline might attenuate the rewarding effects of nicotine-containing e-cigarettes as well, which could hamper the transition. Thus, the study will provide important information about the actions of varenicline on CC as well as e-cigarettes. There is no therapeutic intent in that smokers' nicotine/tobacco dependence will not be treated; the goal is to switch from one form of nicotine/tobacco dependence (CC) to dependence on a different tobacco product (e-cigarettes).

1.2 BACKGROUND

The burden of disease and death attributable to combustible cigarette (CC) smoking is enormous, with an estimated 540,000 premature deaths annually in the United States [1]. Considerable progress has been made toward reducing the prevalence of smoking, through education about the harms of smoking, increased taxation/regulation and the greater availability of cessation treatments. However, despite a gradual reduction in smoking prevalence over the years, in 2015, 15% of the adult U.S. population, or 35 million individuals, continued to smoke [2].

The 2010 U.S. Surgeon General's Report [3] implicated combustion products, rather than nicotine, in contributing to the major smoking-related diseases. Therefore, e-cigarettes may reduce health risks to the user by avoiding combustion. Instead, they heat a solution (usually a mixture of propylene glycol and glycerol) that also contains nicotine and flavorings, in order to generate an aerosol at much lower temperatures than burning cigarettes [4]. Measures of constituents in e-cigarette aerosol show substantial reductions in most toxicants, including carbon monoxide, carcinogens (including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons), and volatile organic compounds such as acrolein, acrylamide, acrylonitrile, 1,3-butadiene and ethylene oxide [5, 6]. This reduction in toxicant yield could potentially translate into a marked reduction in risk to the smoker. Recent studies of smokers and e-cigarette users have shown 90-100% reductions in many of the harmful and potentially harmful constituents of cigarette smoke [7]. Preliminary studies also indicate improvements in lung function among e-cigarette users [8]. However, many smokers continue to smoke combustible cigarettes along with using e-cigarettes, which undermines any reduction in health risks that might be achieved. Hence, it is important to identify methods to facilitate the complete switching from CC to e-cigarettes.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 COMPLETE SWITCHING FROM CC TO HALO G6

The primary switching outcome will be smoking abstinence during weeks 8-11 post-quit date. This will be defined as self-report of no cigarette smoking (not even a puff), confirmed by an expired air CO reading of less than 5 ppm.

2.2 POINT ABSTINENCE (FROM CC) AT SIX MONTHS POST SWITCH

A secondary outcome will be 7-day point abstinence at 6 months post-switch. Assessed by self-report utilizing an automated SMS messaging system.

2.3 CHANGE IN ANKLE-BRACHIAL INDEX (ABI)

The Ankle-Brachial Index (ABI) is the most common test used for screening and detection of Peripheral Arterial Disease (PAD) in the clinical setting. The ABI is the ratio of highest systolic blood pressure obtained from the brachial arteries (arms) versus the highest systolic blood pressure obtained from the posterior tibial or dorsalis pedis arteries (ankles/feet).

This study will utilize this simple test to evaluate changes in arterial flow when smokers change from combustible cigarettes to electronic cigarettes over a 13-week period. Measurements will be obtained using a manual sphygmomanometer and an 8- to 10- MHz doppler ultrasound probe. Subjects will undergo this testing at Visit 1 (baseline data) and at the end of study (Visit 7). All values will be reviewed by licensed medical providers. Subjects with values indicative of mild to moderate peripheral artery disease (less than 0.90, but greater than 0.40) will be referred to their primary care provider for follow up and will be enrolled in the study. Subjects with severe disease (less than or equal to 0.40) at baseline will be excluded from the study and referred to their primary care providers [9].

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This single-group, small-scale, open-label study (N= 25 to 50) will evaluate the impact of varenicline on the process of switching from combustible cigarettes (CC) to an e-cigarette. There will be a data collection period of at least five days to obtain baseline data on use of combustible cigarettes. Participants enrolled in the study will receive a G6 e-cigarette at V2 for *ad libitum* use. The FDA approved starter kit of varenicline will be provided to participants at V3 (0.5 mg nightly for days 1-3, then 0.5 mg twice daily for days 4-7) along with additional G6 cartomizers. After the first week of varenicline, participants will receive the FDA-approved standard dose of varenicline (1 mg twice daily) and will continue to receive enough G6 cartomizers to last until their next study visit. Halo G6 and varenicline use will continue until the participant returns for the End-of-Study visit.

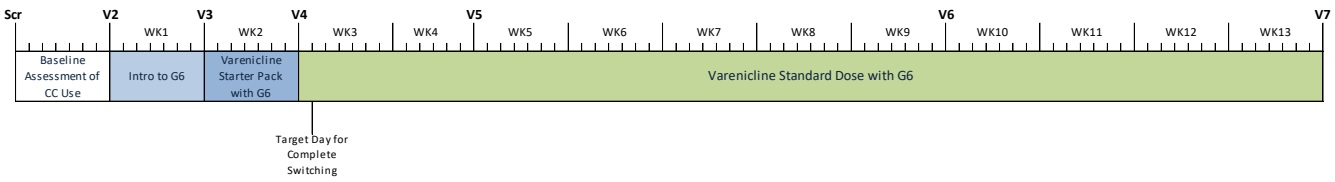


Figure 1 - Overall Study Design

The outcome of varenicline on the process of switching from combustible cigarettes (CC) to an e-cigarette will be compared to the following benchmarks. Initial results will fall into one of the following three categories:

3.1.1 Complete switching rate of 64%

If this study achieves at least a 64% (16/25) switching rate to Halo G6 for the first 25 smokers tested at visit 7, it will be viewed as having considerable promise, and will immediately be advanced to larger-scale (~N=200) randomized controlled clinical trials (RCTs) to provide a rigorous evaluation of its efficacy and effectiveness in helping smokers switch to e-cigarettes. These trials may include both double-blind efficacy trials and unblinded, pragmatic, real-world effectiveness trials. Future trials will be submitted to the Institutional Review Board (IRB) as new protocols.

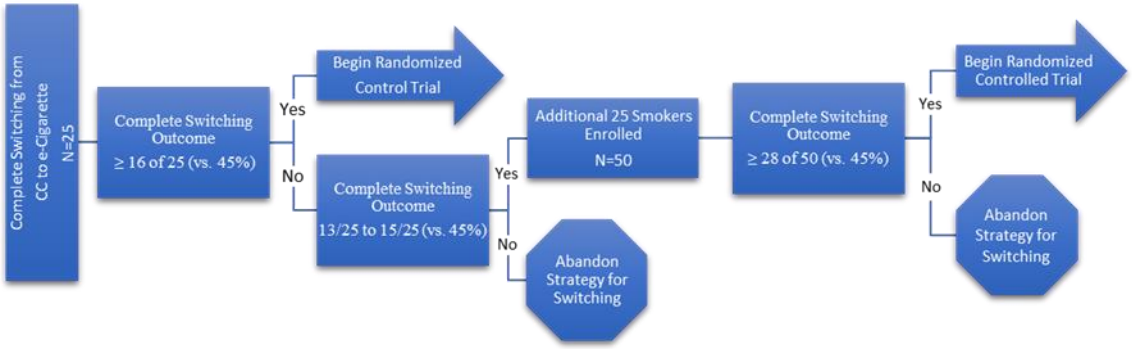
3.1.2 Complete switching rate of 52% to 60%

If this study achieves switching to Halo G6 in 52%-60% (13/25 to 15/25) of the first 25 smokers tested at visit 7, then an additional sample of 25 smokers will be enrolled (total N=50) to obtain a more precise estimate of the switching rate. If, cumulatively, complete switching to G6 is achieved in at least 56% (28/50) at visit 7, the use of varenicline as an aid to switching will then be advanced to larger RCTs.

3.1.3 Switching Thresholds Not Achieved

If either of the above switching rate thresholds is not met in the first 25-50 smokers tested, the use of varenicline as an aid to switching will be considered unpromising, and further subjects will not be enrolled.

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 procedure is discarded prematurely, would be approximately 20%. The diagram below depicts the stepwise evaluation algorithm.



3.2 General Study Procedures

At each session, expired air CO will be measured along with blood pressure, heart rate, respiratory rate and body weight. Participants will also complete questionnaires rating subjective effects of smoking and e-cigarette use. Subjects will be given enough cartomizers to last until their next scheduled session, along with an extra 4 days' worth to allow for flexibility in case sessions need to be rescheduled. E-cigarette usage will be tracked not only by self-reported number of occasions used, but also by cartomizer counts (used or unused).

3.3 Point of Enrollment

Participants will be enrolled after all safety laboratory results have been received and reviewed by the medical staff (MD or PA). The Halo G6 and the cartomizers will be dispensed starting at V2, and at each subsequent visit until the End-Of-Study. Study drugs will be dispensed starting at V3, and at each subsequent visit until the End-Of-Study.

3.4 Study and Session Durations

The total duration for a participant will be approximately 14-16 weeks. The Screening Session (Visit 1) will last approximately 2 ½ to 3 hours. The other study sessions will last approximately one hour.

4 Participant Involvement

4.1 Selection of Study Population

Healthy, cigarette smoking adults, age 21-65 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 21 to 65 years of age (inclusive) at screening.
3. Smokes at least 10 commercially available cigarettes per day (no brand restrictions), for the last 12 months.
4. Has an expired air CO reading of at least 10 ppm at screening.
5. Interested in switching to an electronic cigarette.
6. Willing and able to comply with the requirements of the study.
7. Owns a smart phone with text message and data capabilities compatible with necessary surveys.

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, Ankle-Brachial Index, 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. Planned use of an FDA-approved smoking cessation product during the study.
4. High blood pressure (systolic > 150 mmHg or diastolic >95 mmHg) at screening.
5. Body mass index (BMI) less than 15.0 kg/m^2 or greater than 40.0 kg/m^2.
6. Coronary heart disease, structural cardiac disease (including, but not limited to valvular heart disease or cardiac murmurs), cardiac dysrhythmias, syncope, cardiac chest pain, or history of heart attack or heart failure.
7. Has received psychotherapy or behavioral treatments potentially impacting symptoms of depression, anxiety, or nicotine withdrawal within 30 days of screening, or during the study.
8. Taking antidepressants, psychoactive medications (e.g. antipsychotics, benzodiazepines, hypnotics) or medications that prolong QT_c.
9. Use of any of these products in the past 30 days: a. Illegal drugs (or if the urine drug screen is positive for cocaine, THC, amphetamines, methamphetamines, or opiates); b. Experimental (investigational) drugs that are unknown to subject; c. Chronic opiate use.
10. Use of smokeless tobacco (chewing tobacco, snuff), cigars (except for "Black & Mild" cigars or Cigarillos), pipes, hookah, e-cigarettes, nicotine replacement therapy or other smoking cessation treatments within 14 days of screening.
11. Pregnant or nursing (by self-report) or has a positive pregnancy test.
12. Enrollment requirements met.

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™, 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 will be discontinued from the study for any of the following reasons:

- 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 in the study, as judged by the Investigator or designee.

4.4.2 Subjects may be discontinued from the study for any of the following reasons based on the judgment of the Investigator:

- No-show to appointments and unable to reschedule within the visit window.
- The misuse or abuse of study related equipment.
- Unwilling or unable to comply with study procedures.

4.5 Lost to Follow-up

For subjects lost to follow-up, a reasonable number of attempts to contact the subject (including written correspondence and/or phone calls) will be made and documented in the source documents. The date of the last contact (e.g. last visit, last phone call) will be recorded in the source document. When the PI(s) or designee(s) declare(s) a subject 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 subject.

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 (V1) and $75 at the completion of each study session V2 through V7. Subjects will also receive an additional payment of $5/day for responding to daily text messages during the 13-week product use period.

If subjects are asked by study staff to return to the center to complete or redo parts of the screening in situations of equipment malfunctions or other circumstances that are beyond the subjects' control, subjects may be reimbursed for mileage.

Subjects 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 HALO-G6 ELECTRONIC NICOTINE DELIVERY SYSTEM

5.1 DESCRIPTION OF HALO G6

The Halo G6 is a breath-actuated, rechargeable e-cigarette that comes with prefilled e-liquid cartomizers. This e-cigarette was chosen over other tank-based or pod-based e-cigarette models because of its similarity in shape and size to a cigarette. Because one of the goals is to provide habit substitution for smoking that varenicline cannot provide, this "cigalike" design is considered advantageous.

5.2 DESCRIPTION OF E-LIQUID

Each G6 prefilled cartomizer contains a 50/50 blend nicotine salt with 35mg nicotine strength. The 3.5% nicotine concentration was chosen over higher (e.g. 5%) concentrations to reduce the likelihood of nausea, given that nausea is a side effect of varenicline. The cartomizers come in packs of five. All Halo brand e-liquids undergo independent testing and they are manufactured by Nicopure labs.

This study will use "Tribeca" (tobacco) and "Menthol" flavored cartomizers, with subjects choosing their preferred one of these flavors. At Visit 2, subjects will be allowed to use the two different flavors *ad libitum*, presented in counterbalanced order (randomly assigned), with a 10-minute period between each trial use. Research staff will inquire whether the subjects are willing and able to use the Halo G6 (either flavor) during the study, to determine eligibility.

5.3 PRODUCT USE TIMEFRAME

The maximum amount of time the G6 will be in use will be for 13 weeks, plus up to an additional four days (to allow for the scheduling window). Subjects will be instructed on how to use the e-cigarette prior to dispensing.

5.4 ACCOUNTABILITY AND COMPLIANCE

The G6 will be dispensed by the Investigator or designated study staff, as per study design. Subjects will be dispensed cartomizers initially at 125% based on their daily smoking habits as reported at baseline (one per pack of cigarettes smoked per day). Subjects may come into the office between visits to get additional supplies if needed. Each dispensation and collection of the product will be recorded.

5.4.1 Storage and Accountability

All products will be stored in a locked, limited-access area at the study site and kept at a controlled room temperature (defined as 20 - 25°C [68 - 77°F], with excursions permitted to 15 - 30°C [59 - 86°F]). Halo products should not be exposed to extreme heat or cold.

5.4.2 Compliance

Compliance will be ensured by strict distribution of the product and collection of devices (used and unused) which 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, activating receptors; however, compared to nicotine, varenicline also acts as an antagonist, blocking occupied receptors from additional stimulation from nicotine. Recognized as 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 [10]. Effective treatment of nicotine addiction is essential for reducing the substantial current and predicted morbidity and mortality associated with tobacco smoking. Despite the availability of effective treatments for smoking cessation, such as nicotine replacement therapy and bupropion sustained-release (SR), abstinence rates remain less than optimal. Varenicline is the first in a new class of agents for smoking cessation, the alpha(4)beta(2) nicotinic acetylcholine receptor (nAChR) partial agonists. Nicotine addiction is mediated by stimulation of central alpha(4)beta(2) nAChRs by nicotine, which causes the release of dopamine, ultimately leading to the pleasurable effects of smoking. As a nAChR partial agonist, varenicline attenuates the craving and withdrawal symptoms that occur with abstinence from nicotine and also reduces the rewarding effects of nicotine obtained from smoking in patients who lapse. Thus, varenicline offers a new therapeutic option for the treatment of nicotine addiction. Clinical trials have demonstrated superior efficacy of this agent over placebo and bupropion-SR for achieving abstinence from smoking, and varenicline has also been shown to significantly delay smoking relapse. As the newest agent approved for smoking cessation, the mechanism of action, efficacy, and safety of varenicline. Common adverse events associated with varenicline (occurring 10% or more) include nausea, insomnia, abnormal dreams, headaches, and nasopharyngitis.[11] 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.[12–14]

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, for 11 weeks.

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, in which case the dose will be decreased to 0.5 mg twice a day for moderate to severe side effects). Participants will be re-evaluated within one week 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).

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”.

6.4.2 Storage and Accountability

Varenicline will be stored in a climate-controlled secured-storage site with access limited to the authorized personnel only. Full accountability of the distributed products will be ensured by designated staff.

6.4.3 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.

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 7.5). Study personnel will adhere to standard operating procedures (SOPs) for all activities. Appropriate medical advice will be provided by qualified staff (licensed providers) to the subject in case of any medical findings requiring health care.

7.1 INFORMED CONSENT AND GUIDANCE

Prior to any study assessments being performed, the subject 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 subject for study participation.

Designated staff, under the supervision of the Principal Investigator, will obtain informed consent from each participant. The person obtaining consent provides the participants with a printed document that explains the procedures and risks. Designated staff 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 subjects are expected to complete, we do not recruit potential subjects who do not read, are blind, or who do not understand English. We are not equipped to validate alternate versions of our questionnaires, most of which are not published. Questionnaires cannot be administered orally by a translator or by technicians to illiterate or blind subjects 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 7.5).

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 subject will be around 30 mL for clinical chemistry, hematology, and serum pregnancy (for females).

Samples for clinical chemistry, hematology, and serum pregnancy test will be sent to LabCorp for analysis. Urinalysis will also be performed by LabCorp.

The results of the clinical chemistry, hematology and urine analysis safety panel will not routinely be given to subjects to send or be sent to their physician to include in their medical record. However, if the subject's laboratory results are clinically relevant (including positive pregnancy tests), the research medical staff will send the subject a copy of the laboratory results. Subjects who are accepted into the study but need medical follow-up due to minor abnormalities in laboratory results (at any session) will also receive a copy of the laboratory results.

7.2.1 Safety Laboratory

Safety laboratory includes clinical chemistry, hematology, and urinalysis and will be assessed at Visit 1.

7.2.1.1 *Clinical Chemistry*

Clinical Chemistry	
Sodium	Chloride
Potassium	Carbon dioxide
Blood urea nitrogen (BUN)	Creatinine
Glucose	Calcium
Total protein	Albumin
Bilirubin	Alkaline phosphatase (AP)
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)

7.2.1.2 *Hematology*

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

7.2.2 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 LabCorp 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.

In the event of a positive urine drug test for cocaine, THC, opiates, amphetamines, or methamphetamines at the screening visit (V1), subjects are notified that they have been excluded from study participation because of a positive drug test.

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

Table 1 - Urinalysis Assessments

Drug Screening
Amphetamine
Cocaine
THC
Methamphetamine
Opiates

Table 2 - Drug Screening

7.2.3 Serum Pregnancy Test

Serum pregnancy test will be performed during the screening visit for all females.

Serum Pregnancy Test
Quantitative human chorionic gonadotropin (HCG) test

7.2.4 Urine Pregnancy Test

The urine pregnancy test will be performed by study personnel on site for all females at each visit (except screening).

7.2.5 Electrocardiogram (ECG)

ECG recording will be performed as per the site's standard operating procedures. A standard 12-lead ECG will be recorded after the subject 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. Every ECG has to be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

ECG print-outs will be interpreted by a qualified physician or licensed medical provider. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents and signed by the Investigator or designee.

7.2.6 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate), will be measured in sitting position after the subject has rested for at least 5 minutes. After two minutes of standing, a second blood pressure reading (systolic and diastolic) and pulse rate will be obtained at the screening visit (V1).

7.2.7 Ankle-Brachial Index

Measurements will be obtained using a manual sphygmomanometer and an 8- to 10- MHz doppler ultrasound probe. Subjects will undergo this testing at Visit 1 (baseline data) and at the end of study (Visit 7). All values will be reviewed by licensed medical providers. Subjects with values indicative of mild to moderate peripheral artery disease (less than 0.90, but greater than 0.40) will be referred to their primary care provider for follow up and will be enrolled in the study. Subjects with severe disease (less than or equal to 0.40) at baseline will be excluded from the study and referred to their primary care providers.

7.2.8 Physical Examination

A complete physical examination, including auscultation and palpation will be performed. A complete 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 representative.

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

7.2.9 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 sessions.

7.2.10 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 screening. A concomitant disease is defined as any condition that started prior to screening and is still ongoing at V1 (this may also include findings detected during the screening visit (V1)).

7.2.11 Prior and Concomitant Medication

All medication taken 30 days prior to the screening visit (V1) and during the study will be documented. Medications which are stopped before the screening visit (V1) will be considered as prior medication. Medications which are started prior to the screening visit (V1) and which are still being taken by the subject during the study, as well as medications that are initiated after the screening visit (V1) will be considered as concomitant medications. 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 have to be documented.

7.2.12 Body Height and Body Weight

Body weight will be measured at each visit. Height and weight will be measured at screening, and body mass index (BMI) will be calculated.

7.2.13 Demographics

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

7.2.14 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).

7.2.15 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.

7.2.15.1 *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).

7.2.15.2 *Modified Cigarette Evaluation Questionnaire (mCEQ) and Modified Electronic Cigarette Evaluation Questionnaire (mECEQ)*

The Cigarette Evaluation Questionnaire was initially developed in the PI's laboratory and used in numerous studies to assess the effects of pharmacological treatments on the rewarding effects of cigarette smoking. The mCEQ (Appendix 9) is a widely used and validated questionnaire that will be utilized to assess the degree to which subjects experience the reinforcing of smoking, providing five subscale scores: smoking satisfaction (satisfying, tastes good, enjoy smoking), psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), aversion (dizziness, nauseated), enjoyment of respiratory tract sensations (single-item assessment), craving reduction (single-item assessment). Subjects will be asked to assess the 12 items of the questionnaire on a 7-point scale, ranging from "not at all" to "extremely". The e-cigarette version of this questionnaire (mECEQ, Appendix 10) will also be used.

7.2.15.3 *Reasons to Smoke*

The Reasons to Smoke questionnaire (Appendix 17) is used to determine the most important reasons to smoke for each subject.

7.2.15.4 *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).

7.2.15.5 *ABOUT – Assessment of Behavioral Outcomes*

The ABOUT is a self-report instrument that measures dependence in a directly comparable way across different tobacco- and nicotine-containing products.

7.2.15.6 *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.

7.2.15.7 *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.

7.2.15.8 *Registration Form*

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

7.2.15.9 *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).

7.2.15.10 *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.

7.2.15.11 *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).

7.2.15.12 *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).

7.2.15.13 *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 7.6).

7.3 5-Day Smoking Baseline Collection

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

7.4 6-Month Follow Up

Participants who complete the study will be contacted six months after the complete switch day utilizing an automated SMS messaging system, to ascertain their current smoking status and use of e-cigarettes.

7.5 SCHEDULE OF EVENTS

Visit Assessments and Procedures		Screening Session	5-Day Baseline Cig Data Collection	Laboratory Sessions						Product Use Period 12 Weeks
		V1		V2	V3	V4	V5	V6	V7	PM SMS
	Informed Consent and Guidance	•								
	Inclusion/Exclusion Criteria	•								
	Enrollment/Randomization			•						
	Prior and Concomitant Medication	•		•	•	•	•	•	•	
Questionnaires	Smoking History Questionnaire	•								
	Registration Form	•								
	Employment History			•						
	Medical History/Review of Systems	•								
	Payment Verification Form	•		•	•	•	•	•	•	
	Reasons to Smoke			•					•*	
	Modified Cigarette Evaluation Questionnaire (mCEQ)			•	•	•	•	•	•	
	The Fagerström Test for Nicotine Dependence (FTND)			•	•				•	
	Assessment of Behavioral OUTcomes (ABOUT)			•	•				•	
	Patient Health Questionnaire (PHQ-9)	•		•	•	•	•	•	•	
	e-Cigarette Usage (via daily SMS text)									•
	Smoking Status (via daily SMS text)		•							•
	Safety Laboratories	•								
	Serum Pregnancy Test (Females)	•								
	Urine Pregnancy Test (Females)			•	•	•	•	•	•	
	Urine Drug Screen	•								
	CO Breath Test	•		•	•	•	•	•	•	
	Ankle-Brachial Index (ABI)	•							•	
	ECG	•								
Vitals	Blood Pressure	•		•	•	•	•	•	•	
	Heart rate	•		•	•	•	•	•	•	
	Temperature	•								
	Respiratory rate	•		•	•	•	•	•	•	
	Weight	•		•	•	•	•	•	•	
	Height	•								
	Physical Examination	•		•#	•#	•#	•#	•#	•#	
	Halo Flavor Assessment and Questionnaire			•						
	Collect Used/Unused Halo products				•	•	•	•	•	
	Dispense Halo products			•	•	•	•	•		
	Collect Used/Unused Blister Packs					•	•	•	•	
	Dispense Study Drugs in Blister Packs				•	•	•	•		

Targeted examination as needed

* Based on current product use

7.6 SMS MESSAGING

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

- How soon after you woke 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?

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

- Have you smoked any combustible cigarettes today?
  - If yes, how soon after you woke 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?
- Have you used your e-cigarette today?
  - If yes, how soon after you woke up did you use it?
    1-Within 5 Minutes, 2-6 to 30 Minutes, 3-31 to 60 Minutes, 4-After 60 Minutes
- How many times did you use your e-cigarette today?
- Did you take your study drug this morning? (After Visit 3)
- Did you take your study drug this evening? (After Visit 3)

7.6.3 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 combustible cigarette since your last visit?
  - If yes, are you still smoking combustible cigarettes right now?
  - How many combustible cigarettes do you smoke per day on average?
- Have you used an e-cigarette since your last visit?
  - If yes, are you still using an e-cigarette?
  - How often do you use an e-cigarette?

8 RISK / BENEFIT INFORMATION

8.1 POTENTIAL RISKS

Continuing to smoke carries significant health risks; however, the participants in the studies will have expressed an interest in switching from smoking combustible cigarettes to using an electronic cigarette during the brief study duration, and hence will not be exposed to significant additional risks.

8.1.1 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.[11] The most common adverse reaction reported is nausea, with 30-40% of participants in randomized control trials reporting mild to moderate levels of nausea.[15] Discontinuation/drop-out rates of nearly 10% have been noted during clinical trials due to these adverse

effects.[16] 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.

8.1.2 Use of Halo G6

The common risks associated with e-cigarette use include coughing, dry mouth, throat irritation, sore throat and shortness-of-breath.

8.1.3 Tobacco Withdrawal

To the extent that nicotine or other tobacco smoke constituent intake is reduced or eliminated, participants may experience tobacco withdrawal symptoms, including craving, difficulty concentrating, mood disturbance and increased appetite/weight gain.

8.1.4 Nicotine Toxicity

The e-cigarette may deliver less of various tobacco smoke constituents than participants' usual brands of cigarettes, and in some cases, may deliver more nicotine. However, participants control their nicotine intake and many studies have shown that smokers effectively limit their nicotine intake from cigarettes to avoid symptoms of nicotine toxicity (e.g., nausea, vomiting, sweating, headache, dizziness, jittery, palpitations, or in the case of extreme cases of nicotine overdose, convulsions, respiratory paralysis and death).

8.1.5 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.

8.2 Protection Against Risks

The risks to which participants will be exposed are comparatively minor, because it is unlikely when using the e-cigarette that they will be exposed to higher levels of toxicants than when smoking their cigarettes. Smokers are very experienced in regulating their nicotine intake to avoid excessive amounts [17]. Additionally, participants will be screened medically and monitored throughout the study.

Study participants will receive detailed instructions on the use of the tobacco products distributed to them, in order to minimize the possibility of misuse. Subjects will be instructed to keep all nicotine/tobacco products away from children and pets.

Participants will be instructed to report any side effects to study staff, who will communicate these reports to the medical staff. The most appropriate course of action will be determined, which may include options for termination of exposure to study-related clinical materials (e.g., e-cigarettes), options for dose reductions to varenicline, or complete termination of varenicline. Participants will, however, be reminded that they have the option to withdraw from the study at any time. Subjects will also be given a 24-hour emergency contact number in the event that side effects or adverse events occur between sessions.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 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.

9.2 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.

10 REPORTING OF ADVERSE EVENTS

10.1 DEFINITIONS

10.1.1 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.

10.1.2 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.

10.2 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 face-to-face interviews with the subject.

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.

10.2.1 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.

All ongoing AEs at the end of study participation will be followed-up by the Investigator or designee until they have improved, resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found. The Investigator or designee will refer the subject to their Primary Care Provider for follow up of those AE when appropriate.

10.3 Assessment of Adverse Events

10.3.1 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.

10.3.2 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.

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

All ongoing Non-Serious AEs at the end of study participation will be followed-up by the Investigator or designee until they have improved, resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found. The Investigator or designee will refer the subject to their Primary Care Provider for follow up of those AE when appropriate.

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).

10.5 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.

10.6 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.

10.7 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 according to local regulations.

10.8 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.

11 Data Management

11.1 Data Collection Procedures

The results from the clinical assessments will be recorded in the source data file by the Investigator or their authorized designee and then captured in the case report forms (CRFs), unless specified otherwise in the final protocol. 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 and transferring the data to the CRFs.

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, reason for change, and identification of the person making the change. CRF data will be verified against the source documents at the study site by appropriate staff. Instances of missing or unclear data will be discussed with the Investigator for resolution.

11.2 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.

11.3 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.

11.3.1 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.

11.3.2 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.

11.3.3 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.

11.3.4 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.

11.4 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 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.

12.1 OUTCOMES

12.1.1 Switching Outcome

Complete switching from combustible cigarette use 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 switching outcome will be smoking abstinence during weeks 8-11 post-switching 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 smoked during weeks 8-11 will be counted as having not completely switched to e-cigarette use. A secondary outcome will be 7-day point abstinence at 6-months post-switch. The main goal of the 6-month follow-up is to assess the persistence of switching to e-cigarettes for those who do switch (even partially) during the first 11 weeks. The main hypothesis to be evaluated in this pilot study is that the rate of complete switching to e-cigarette use will be greater than the historical benchmark of 45% smoking abstinence expected with varenicline when it is used in smoking cessation treatment.

12.1.2 Ankle-Brachial Index (ABI)

The ABI is the ratio of highest systolic blood pressure obtained from the brachial arteries (arms) versus the highest systolic blood pressure obtained from the posterior tibial or dorsalis pedis arteries (ankles/feet). It is a simple test, requiring minimal operator training. The ABI has been shown to be a marker of atherosclerosis, as well as a predictor of mortality [18]. A study from 1999 by Yataco and Gardner demonstrated acute changes in ABI's in chronic smokers with peripheral arterial occlusive disease (PAD) after smoking just two of their usual brand combustible cigarettes [19]. Another study published in 2013 demonstrated statistically significant improvements in ABIs at 12 months for subjects who quit smoking, which the authors associated with improved arterial stiffness with smoking cessation [20]. We propose to utilize this simple test to evaluate vascular changes when smokers change from combustible cigarettes to electronic cigarettes over a 13-week period. The ABI test could provide valuable information regarding macrovascular effects, including changes in arterial stiffness, associated with switching from a combustible cigarette to an electronic cigarette. It is hypothesized that the ABIs of participants who completely switch to e-cigarettes will increase, demonstrating an acute improvement in peripheral circulation after avoidance of the deleterious effects from inhaled combustible cigarette smoke.

12.2 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.

13 ETHICS AND REGULATIONS

13.1 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.

13.2 INVESTIGATIONAL NEW DRUG APPLICATION

An Investigational New Drug (IND) application is not required for use of varenicline in this study. 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.

An Investigational New Drug (IND) application is not required for use of Halo G6 in this study because the G6 is not intended for use as a smoking cessation aid.

13.3 INVESTIGATIONAL TOBACCO PRODUCT APPLICATION

An Investigational Tobacco Product (ITP) application is not required for use of the Halo G6 in this study. The device and the cartomizers were marketed prior to August 8, 2016 and are not being modified for the investigation.

13.4 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.

13.5 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.

13.6 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).

14 Administrative Considerations

14.1 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.

14.2 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.

15 REFERENCES

1. Carter, B.D., Freedman, N.D., Jacobs, E.J.: Smoking and mortality--beyond established causes. N. Engl. J. Med. 372, 2170 (2015). https://doi.org/10.1056/NEJMc1503675
2. Ward, B.W.: Early Release of Selected Estimates Based on Data From the 2015 National Health Interview Survey (05/2016). 120 (2015)
3. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US): How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA) (2010)
4. Geiss, O., Bianchi, I., Barrero-Moreno, J.: Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. Int. J. Hyg. Environ. Health. 219, 268–277 (2016). https://doi.org/10.1016/j.ijheh.2016.01.004
5. McRobbie, H., Phillips, A., Goniewicz, M.L., Smith, K.M., Knight-West, O., Przulj, D., Hajek, P.: Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. Cancer Prev. Res. Phila. Pa. 8, 873–878 (2015). https://doi.org/10.1158/1940-6207.CAPR-15-0058
6. Tayyarah, R., Long, G.A.: Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. Regul. Toxicol. Pharmacol. RTP. 70, 704–710 (2014). https://doi.org/10.1016/j.yrtph.2014.10.010
7. Goniewicz, M.L., Smith, D.M., Edwards, K.C., Blount, B.C., Caldwell, K.L., Feng, J., Wang, L., Christensen, C., Ambrose, B., Borek, N., Bemmel, D. van, Konkel, K., Erives, G., Stanton, C.A., Lambert, E., Kimmel, H.L., Hatsukami, D., Hecht, S.S., Niaura, R.S., Travers, M., Lawrence, C., Hyland, A.J.: Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. JAMA Netw. Open. 1, e185937–e185937 (2018). https://doi.org/10.1001/jamanetworkopen.2018.5937
8. Polosa, R., Morjaria, J.B., Prosperini, U., Russo, C., Pennisi, A., Puleo, R., Caruso, M., Caponnetto, P.: Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. Int. J. Chron. Obstruct. Pulmon. Dis. 13, 2533–2542 (2018). https://doi.org/10.2147/COPD.S161138
9. Aboyans, V., Criqui, M.H., Abraham, P., Allison, M.A., Creager, M.A., Diehm, C., Fowkes, F.G.R., Hiatt, W.R., Jönsson, B., Lacroix, P., Marin, B., McDermott, M.M., Norgren, L., Pande, R.L., Preux, P.-M., Stoffers, H.E.J., Treat-Jacobson, D., American Heart Association Council on Peripheral Vascular Disease, Council on Epidemiology and Prevention, Council on Clinical Cardiology, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia: Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 126, 2890–2909 (2012). https://doi.org/10.1161/CIR.0b013e318276fbcb
10. Hays, J.T., Ebbert, J.O., Sood, A.: Efficacy and safety of varenicline for smoking cessation. Am. J. Med. 121, S32-42 (2008). https://doi.org/10.1016/j.amjmed.2008.01.017
11. Hays, J.T., Ebbert, J.O., Sood, A.: Efficacy and safety of varenicline for smoking cessation. Am. J. Med. 121, S32-42 (2008). https://doi.org/10.1016/j.amjmed.2008.01.017
12. Halperin, A.C., McAfee, T.A., Jack, L.M., Catz, S., McClure, J.B., Deprey, M., Richards, J., Zbikowski, S., Swan, G.E.: IMPACT OF SYMPTOMS EXPERIENCED BY VARENICLINE USERS ON TOBACCO TREATMENT IN A REAL WORLD SETTING. J. Subst. Abuse Treat. 36, 428–434 (2009). https://doi.org/10.1016/j.jsat.2008.09.001

13. Varenicline Side Effects in Detail, https://www.drugs.com/sfx/varenicline-side-effects.html
14. Research, C. for D.E. and: Drug Safety and Availability - FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of cardiovascular adverse events, https://www.fda.gov/Drugs/DrugSafety/ucm330367.htm
15. CHANTIX® (varenicline tartrate) | Pfizer Medical Information - US, https://www.pfizermedicalinformation.com/en-us/chantix
16. Swan, G.E., Javitz, H.S., Jack, L.M., Wessel, J., Michel, M., Hinds, D.A., Stokowksi, R.P., McClure, J.B., Catz, S.L., Richards, J., Zbikowski, S.M., Deprey, M., McAfee, T., Conti, D.V., Bergen, A.W.: Varenicline for Smoking Cessation: Nausea Severity and Variation in Nicotinic Receptor Genes. Pharmacogenomics J. 12, 349–358 (2012). https://doi.org/10.1038/tpj.2011.19
17. Delnevo, C.D., Giovenco, D.P., Steinberg, M.B., Villanti, A.C., Pearson, J.L., Niaura, R.S., Abrams, D.B.: Patterns of Electronic Cigarette Use Among Adults in the United States. Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob. 18, 715–719 (2016). https://doi.org/10.1093/ntr/ntv237
18. Miller, D., Pearsall, E., Johnston, D., Frecea, M., McKenzie, M., Ontario Provincial ERAS Enterostomal Therapy Nurse Network: Executive Summary: Enhanced Recovery After Surgery: Best Practice Guideline for Care of Patients With a Fecal Diversion. J. Wound Ostomy Cont. Nurs. Off. Publ. Wound Ostomy Cont. Nurses Soc. 44, 74–77 (2017). https://doi.org/10.1097/WON.0000000000000297
19. Yataco, A.R., Gardner, A.W.: Acute reduction in ankle/brachial index following smoking in chronic smokers with peripheral arterial occlusive disease. Angiology. 50, 355–360 (1999). https://doi.org/10.1177/000331979905000501
20. Yu-Jie, W., Hui-Liang, L., Bing, L., Lu, Z., Zhi-Geng, J.: Impact of smoking and smoking cessation on arterial stiffness in healthy participants. Angiology. 64, 273–280 (2013). https://doi.org/10.1177/0003319712447888

Appendix 1 - 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 2 – 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 3 - 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 4 – 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

Have you been a regular smoker for the past year?
○ Yes ○ No

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 participated in a smoking study in the past?
○ Yes ○ No

If YES, when? _____ Where? _____

8. Are you interested in switching from a combustible cigarette to an electronic cigarette?
○ Yes ○ No

9. Have you smoked cigar in the past 14 days?
○ Yes ○ No

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

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

12. Have you used experimental or investigational drugs in the past 30days?
○ Yes ○ No

Appendix 5 – 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 6 – 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:	

Office use only:

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 "itchiness"):

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/tabs/pills) and **Route** (oral, topical)	**Frequency** (times per day)	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 7- 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
- ❑ Fatigue/ Lack of energy
- ❑ Fever or chills
- ❑ Weakness
- ❑ Trouble Sleeping

Skin: *(____ none of these apply)*
- ❑ Rashes
- ❑ Lumps
- ❑ Itching
- ❑ Dryness
- ❑ Color changes
- ❑ 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
- ❑ Specks
- ❑ Blurry or double vision
- ❑ Flashing lights
- ❑ Redness
- ❑ Pain

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

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

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

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

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

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

Urinary: *(____ none of these apply)*
- ❑ Frequency
- ❑ Urgency
- ❑ Blood in urine
- ❑ Pain with urination
- ❑ Change in urinary strength
- ❑ 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
- ❑ Stiffness
- ❑ Back pain
- ❑ Redness of joints
- ❑ Swelling of joints
- ❑ Trauma

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

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

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

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

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

Office Use Only

_____ MD/ PA Signature

_____ Date

Appendix 8 – 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

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 9 – modified Cigarette Evaluation Questionnaire (mCEQ)

CIGARETTE EVALUATION QUESTIONNAIRE - modified

Have you smoked any cigarettes since your last visit?

- ❍ No: Skip questionnaire
- ❍ Yes: Please answer the following questions based on the **FIRST** cigarette you smoked on the last day you smoked.

	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?	❍	❍	❍	❍	❍	❍	❍

Page 1 of 1

Appendix 10 – modified Electronic Cigarette Evaluation Questionnaire (mECEQ)

ELECTRONIC CIGARETTE EVALUATION QUESTIONNAIRE - modified

Have you used any ELECTRONIC cigarettes since your last visit?

- ❍ No: Skip questionnaire
- ❍ Yes: Please answer the following questions based on the **FIRST** ELECTRONIC cigarette you used on the last day you used the ELECTRONIC cigarette.

	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 vapor in your throat and chest?	❍	❍	❍	❍	❍	❍	❍
11. Did it immediately reduce your craving for cigarettes?	❍	❍	❍	❍	❍	❍	❍
12. Did you enjoy using the ELECTRONIC cigarette?	❍	❍	❍	❍	❍	❍	❍

Appendix 11 – Halo G6 Flavor Assessment Questionnaire

HALO G6 Flavor Assessment Questionnaire

Now that you have tried the two flavors of HALO G6, are you willing to switch to either of these flavors?

(CHECK ONE RESPONSE ONLY)

YES_____ No_____

If YES, which flavor would you like to use:

Tribeca (tobacco)_____ Mint_____

_____

Participant's Signature and Date

Appendix 12 – 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 13 – SMS Baseline Cigarette Data Collection Survey (after screening – prior to V2)

1. 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 smoked today?

Appendix 14 – SMS Daily Survey

* 1. Have you smoked any combustible cigarettes today?

- ◯ Yes
- ◯ No

2. 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

* 3. How many cigarettes did you smoked today?

* 4. Have you used your e-cigarette today?

- ◯ Yes
- ◯ No

5. How soon after you woke up did you use it?

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

* 6. How many times did you use your e-cigarette today?

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

- ◯ Yes
- ◯ No
- ◯ N/A (Have not received study meds)

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

- ◯ Yes
- ◯ No
- ◯ N/A (Have not received study meds)

Appendix 15 – 6-Month Follow Up Survey

* 1. Hello
Have you smoke a combustible cigarette since your last visit?

- ◯ Yes
- ◯ No

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

- ◯ Yes
- ◯ No

* 3. How many combustible cigarettes do you smoke per day on average?

[ ]

* 4. Have you used an e-cigarette since your last visit?

- ◯ Yes
- ◯ No

* 5. If yes, are you still using an e-cigarette?

- ◯ Yes
- ◯ No

* 6. How often do you use an e-cigarette?

[ ]

Appendix 16 – Assessment of Behavioral OUTcomes (ABOUT)

ASSESSMENT of BEHAVIORAL OUTcomes (ABOUT)

Related to Tobacco and nicotine products

The next questions ask about your experience with tobacco and nicotine products. Please answer all questions. Please think about all the tobacco and nicotine products that you use as you answer all of the following questions.

1. Over the **past 7 days**, on average, how soon after you woke up did you use your first product?

0 to 5 minutes	☐
6 to 15 minutes	☐
16 to 30 minutes	☐
31 to 60 minutes	☐
More than 1 hour to 3 hours	☐
More than 3 hours	☐

2. Over the **past 7 days**, on average, how long before going to sleep did you use your last product?

0 to 5 minutes	☐
6 to 15 minutes	☐
16 to 30 minutes	☐
31 to 60 minutes	☐
More than 1 hour to 3 hours	☐
More than 3 hours	☐

ASSESSMENT of BEHAVIORAL OUTcomes (ABOUT)

Related to Tobacco and nicotine products

3. Currently…	Not at all	A little	Moderately	Very Much	Extremely
a. How much do you feel you need your product(s) to function "normally"?	❍	❍	❍	❍	❍
b. How difficult do you think it would be for you to completely quit your product(s)?	❍	❍	❍	❍	❍

4. Over the past 7 days, how often did you…	Never	Rarely	Sometimes	Most of the time	All the time
a. Have a strong desire to use your product(s)?	❍	❍	❍	❍	❍
b. Use more of your product(s) than you intend to?	❍	❍	❍	❍	❍
c. Feel that you "HAD to have one"?	❍	❍	❍	❍	❍
d. Use your product(s) in a situation where you weren't supposed to?	❍	❍	❍	❍	❍
e. Find it hard to control the need or urge to use your product(s)?	❍	❍	❍	❍	❍
f. Sneak off to use your product(s)?	❍	❍	❍	❍	❍
g. Avoid an activity because you couldn't use your product(s)?	❍	❍	❍	❍	❍
h. Stop what you were doing to use your product(s)?	❍	❍	❍	❍	❍

Appendix 17 – Session Payment Form

For your time and inconvenience related to your participation in this study, you will be paid up to a total of $950 if you complete this study. If you do not complete the study, for any reason, you will be paid for the study visits you do complete according to the following schedule:

- You will receive $25 for completing Study Visit 1.
- You will receive $75 for completing Study Visit 2 through Study Visit 7 ($450 total)
- You will receive $5 for responding to each text message during the study (once per day for approximately 91 - 95 days = approximately $475). In order to receive compensation for each message, you will need to answer all of questions before you receive your next text message.

SESSION PAYMENT LOG

SESSION	DATE ATTENDED	AMOUNT ELIGIBLE VISIT	AMOUNT ELIGIBLE SMS	AMOUNT TO BE PAID	RRC INITIALS	PARTICIPANT INITIALS	DATE PROCESSED
Visit 1-Screen		$25	$0				
Visit 2		$75	$0				
SMS			☐ x $5				
Visit 3		$75					
SMS			☐ x $5				
Visit 4		$75					
SMS			☐ x $5				
Visit 5		$75					
SMS			☐ x $5				
Visit 6		$75					
SMS			☐ x $5				
Visit 7		$75					
SMS			☐ x $5				
TOTAL		$475					

I certify that the payment eligibility process has been fully explained to me and I agree with and accept all conditions of the payment eligibility process.

_____ _____

Participant Signature Date

_____ _____

Research Personnel's Signature Date

Appendix 18 – Reasons To Smoke

REASONS TO SMOKE

Have you smoked any cigarettes since your switch day?

- ❍ No: Skip questionnaire
- ❍ Yes: Please answer the following questions based on the **FIRST** cigarette you smoked on the last day you smoked.

INSTRUCTIONS: Listed below are thirteen common reasons why people like to smoke. Using the scale on the right, fill in the bubble for each statement which most closely describes how important that reason is to you.

	Least Important	Hardly Important	Not Really Important	A Little Important	More Important	Really Important	Most Important
1. It calms me down	❍	❍	❍	❍	❍	❍	❍
2. It gives me something to do with my hands	❍	❍	❍	❍	❍	❍	❍
3. I like the taste and smell	❍	❍	❍	❍	❍	❍	❍
4. I like the sensations deep in my throat or chest	❍	❍	❍	❍	❍	❍	❍
5. It wakes me up when I am drowsy	❍	❍	❍	❍	❍	❍	❍
6. I like to watch the smoke	❍	❍	❍	❍	❍	❍	❍
7. It makes relaxing seem even better	❍	❍	❍	❍	❍	❍	❍
8. It satisfies my craving	❍	❍	❍	❍	❍	❍	❍
9. It gives me a rush	❍	❍	❍	❍	❍	❍	❍
10. It gives me more confidence around other people	❍	❍	❍	❍	❍	❍	❍
11. It helps me control my weight	❍	❍	❍	❍	❍	❍	❍
12. It's is like a friend	❍	❍	❍	❍	❍	❍	❍
13. It helps me concentrate	❍	❍	❍	❍	❍	❍	❍