Pilot Study on

Varenicline in Light and Intermittent Smokers

A Supportive Care-Drug Intervention Study

DUKE CANCER INSTITUTE

A National Cancer Institute-designated Comprehensive Cancer Center

Sponsor-Investigator:	Dr. James Davis – Duke Cancer Institute
Funding Source:	Duke Cancer Institute
Protocol Source:	Dr. James Davis - Duke Cancer Institute
Duke IRB#:	Pro00103506
NCT ID:	NCT04089982

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2. PROTOCOL SYNOPSIS AND RESEARCH SUMMARY

2.1. PURPOSE

Product Name: Varenicline

Development Phase: Phase 1

Protocol Title: Pilot Study on Varenicline in Light and Intermittent Smokers

The overarching goal of this proposal is to assess varenicline with and without cue-extinction therapy for their effect on decreasing cue reactivity in light and intermittent smokers.

Aim 1 - Cue Reactivity

1. **Lab-Based Cue Reactivity:** To determine whether varenicline vs. placebo shows greater reduction in laboratory-based smoking cue reactivity assessed over multiple time points (baseline (4-weeks pre- target quit day(TQD)), 2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD). Lab-based cue reactivity will be assessed at each visit through a laboratory based cue-reactivity assessment paradigm in which the participant is presented with blocks of visual images and after each block is asked to provide a self-report of cigarette craving.

2. **Real-World Cue Reactivity:** To determine whether varenicline vs. placebo shows greater reduction of cue reactivity during "real-world" testing through daily text-based responses over the 6-week study period: 4 weeks prior to the TQD and 2 weeks after the TQD. Real world cue reactivity will be assessed each day through participant texting the study application. Participants will be asked to send a text after each cigarette they smoke, when they experience a craving, and at the end of each day.

Aim 2 - Smoking Abstinence and Reduction

3. **Smoking Abstinence:** To determine whether varenicline is more effective than placebo for achieving 7-day point prevalence smoking abstinence at the 2-weeks post-TQD day visit. Abstinence will be defined as self-report of no smoking for the last 7 days, CO breath test < 7 ppm, and salivary cotinine under 14 ng/ml.

4. **Smoking Reduction:** To determine whether varenicline is more effective than placebo for smoking reduction over the 4-week pre-TQD smoking period and over the 2 week post-TQD period. Smoking reduction will be assessed in three ways: 1. Daily end-of-the-day text messages in which participants provide a self-report of how many cigarettes they smoked that day (in addition to paper self-report diaries), 2. CO breath testing at each study visit, and 3. Salivary cotinine testing at each study visit.

Aim 3 – Medication Adherence and Tolerability

5. **Adherence:** To determine whether varenicline has acceptable adherence when compared to placebo in this population. Medication adherence will be measured using daily text-based assessment of medication use and paper self-report diaries.

6. **Tolerability:** To determine tolerability through participant self-report on an open-ended question on potential self-effects asked at baseline and at each study visit.

Aim 4 - Moderators and Mediators (exploratory)

7. **Baseline Variables (Treatment Moderators):** To determine whether a variety of baseline variables (age, gender, sex, race, nicotine dependence, anxiety, depression, stress, baseline smoking enjoyment) are associated with differential treatment response between varenicline and placebo described within objectives 1-4. For example, does age predict the capacity for varenicline to reduce cue reactivity as measured in a laboratory setting or real-world setting, or the capacity for varenicline to induce smoking abstinence or reduction.

8. **Cue Variables (Treatment Moderators):** To determine whether a variety of experiential or environmental variables (stress level, frustration, anger, sadness, boredom, positive affect, social interaction, time of day, familiar smoking place, smells, visual stimuli, alcohol use) are associated with our primary the intensity of cue reactivity for a particular cue and with smoking on a particular day. The frequency and intensity reported on these variables will also be assessed as treatment moderators – i.e. for their association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

9. **Adherence (Moderator):** To determine whether adherence to varenicline is associated with outcomes across multiple time points (2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD). Medication adherence will be measured using daily text-based questions and self-report diaries, and will be assessed for an association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

10. **Change in Reward (Mediators):** To determine whether changes (baseline to each time point) in physical smoking satisfaction, pleasure from smoking or other forms of "smoking reward" are associated with differential treatment response in objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

Hypotheses

This protocol is hypothesis-supporting and hypothesis-testing.

Aim 1 - Cue Reactivity

1. **Lab-Based Cue Reactivity:** Varenicline vs. placebo will show a greater reduction in laboratory-based smoking cue reactivity assessed over multiple time points (baseline (4-weeks pre-TQD), 2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD). Lab-based cue reactivity will be assessed at each visit through a laboratory based cue-reactivity assessment paradigm in which the participant is presented with blocks of visual images and after each block is asked to provide a self-report of cigarette craving.

2. **Real-World Cue Reactivity:** Varenicline vs. placebo will show a greater reduction of cue reactivity during "real-world" testing through daily text-based responses over the 6-week study period: 4 weeks prior to the TQD and 2 weeks after the TQD. Real world cue reactivity will be assessed each day through participant texting the study application. Participants will be asked to send a text after each cigarette they smoke, whenever they experience a craving, and at the end of each day.

Aim 2 - Smoking Abstinence and Reduction

3. **Smoking Abstinence:** Varenicline vs. placebo will show higher 7-day point prevalence smoking abstinence at the 2-weeks post-TQD day visit. Abstinence will be defined as self-report of not smoking for the last 7 days, CO breath test < 7 ppm, and salivary cotinine under 14 ppm.

4. **Smoking Reduction:** Varenicline vs. placebo will show greater smoking reduction over the 4-week pre-TQD smoking period and over the 2-weeks post-TQD period. Smoking reduction will be assessed in three ways: 1. Daily end-of-the-day text messages in which participants provide a self-report of how many cigarettes they smoked that day (in addition to paper self-report diaries), 2. CO breath testing at each study visit, and 3. Salivary cotinine testing at each study visit.

Aim 3 – Medication Adherence and Tolerability

5. **Adherence:** Varenicline will show acceptable adherence when compared to placebo in this population (adherence to varenicline will not be significantly lower than placebo). Medication adherence will be measured using daily text-based assessment of medication use and paper self-report diaries.

6. **Tolerability:** Varenicline will show good tolerability (the total incidence of study related side effects will not be higher than placebo). Side effects will be measured by self-report in an open-ended question at baseline and at each study visit.

Aim 4 - Moderators and Mediators (exploratory)

7. **Baseline Variables (Treatment Moderators):** A variety of baseline variables (age, gender, sex, race, nicotine dependence, anxiety, depression, stress, baseline smoking enjoyment) are associated with differential treatment response between varenicline and placebo described within objectives 1-4. For example, does age predict the capacity for varenicline to reduce cue reactivity as measured in a laboratory setting or real-world setting, or the capacity for varenicline to induce smoking abstinence or reduction.

8. **Cue Variables (Treatment Moderators):** A variety of experiential or environmental variables (stress level, frustration, anger, sadness, boredom, positive affect, social interaction, time of day, familiar smoking place, smells, visual stimuli, alcohol use) are associated with our primary the intensity of cue reactivity for a particular cue and with smoking on a particular day. The frequency and intensity reported on these variables will also be assessed as treatment moderators – i.e. for their association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

9. **Adherence (Moderator):** We will explore whether adherence to varenicline is associated with outcomes across multiple time points (2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD). Medication adherence will be measured using daily text-based questions (in addition to paper self-report diaries) and will be assessed for an association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

10. **Change in Reward (Mediators):** We will explore a whether changes (baseline to each time point) in physical smoking satisfaction, pleasure from smoking or other forms of "smoking reward" are associated with differential treatment response in objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).

2.2. BACKGROUND AND SIGNIFICANCE

1. Overarching Aim: The overarching aim of this study is to improve our understanding of the neurobehavioral mechanisms among smokers who are driven to smoke primarily by conditioned cues rather than nicotine withdrawal.

Heavy smokers appear to smoke due to nicotine withdrawal and also cues, whereas light and intermittent smokers (LITS) appear to smoke primarily due to cues.[1] Heavy smokers commonly experience nicotine withdrawal symptoms an hour or two after smoking each cigarette, and smoke regularly throughout the day to avoid withdrawal symptoms.[2] On the other hand, LITS (≤10 cigarettes per day or on some days) typically do not experience nicotine withdrawal, and thus, primarily smoke in response to smoking cues (cue-based smoking).[3] The neurobiological basis of cue-based smoking is "cue reactivity," a desire to smoke in response to smoking cues.[4] This is initially learned by pairing smoking cues with smoking (nicotinic reward), and is maintained through repeated pairing of smoking cues and smoking.[4] A number of medications have been used to help LITS quit smoking but mostly none have not been successful.[5] One promising mechanistic pathways through which we may be able to decrease cue reactivity in LITS is nicotinic receptor antagonism - blocking nicotinic reward during smoking should decrease cue reactivity. Varenicline blocks nicotinic receptors and is known to decrease nicotinic reward.[6] Thus, in this study we will assess the effects of varenicline on changes in cue reactivity in LITS.

2. There is a need for effective treatment for light smoking. As we work toward eliminating tobacco use, we need to assess and develop strategies that meet the needs of our current population of smokers. In the past, the smoking population was dominated by heavy smokers, but many heavy smokers have now quit or reduced their smoking such that the majority of smokers today can be classified as either light daily smokers (smoking ≤ 10 cigarettes per day) or non-daily/intermittent smokers (smoking ≤ 10 cigarettes non-daily/intermittently).[7,8] Compared to non-smokers, smoking even one cigarette per day, whether daily or less, increases the risk of morbidity and mortality by nearly 50%.[1,9–13] The motivations for smoking are different for light or intermittent smokers (LITS) than for those that are smoking more heavily. Heavy smokers typically experience nicotine withdrawal throughout the day and smoke regularly to avoid withdrawal symptoms.[1] The half-life of nicotine is roughly 2 hours,[2] and those who experience nicotine withdrawal, such as heavy smokers, tend to smoke every 1-2 hours while awake to maintain sufficiently high serum nicotine in an attempt to avoid withdrawal symptoms. Heavy smokers also respond to smoking cues (cue reactivity), such that when a smoking cue arises they will often smoke an additional cigarette to overcome the cue-associated craving.[14,15] On the other hand, LITS typically do not experience significant nicotine withdrawal symptoms during periods of smoking abstinence.[7,16,17] As a result, LITS do not smoke throughout the day to avoid withdrawal symptoms but instead smoke primarily in response to smoking cues.[16,18] Dr. Saul Shiffman posited a "two-factor model" in which two factors primarily motivate smoking: 1) avoidance of nicotine withdrawal, and 2) in response to smoking cues.[18] In this model, cues might be sensory (sight or smell of tobacco), social (interaction with a friend who smokes), affective (both negative and positive emotions), associative (always smoke with coffee), or contextual (situations in which multiple cues are present).[18] Interestingly, cue-induced craving for nicotine in LITS is just as intense as it is in heavy smokers.[18] Accordingly, when LITS smoke due to cues, nicotine levels achieved are just as high as in heavy smokers,[19] and have almost as much difficulty quitting smoking as do heavy smokers.[18,19]

3. The disease population: Smoking is the leading cause of preventable morbidity and mortality in the US.[8,9] Smoking causes 480,000 deaths per year[10] and is the cause of 28.6% of all cancer-related deaths.[20] Perhaps more striking is that for every death caused by smoking, 30 smokers will live with a severe smoking related illness, including lung disease, heart disease, peripheral vascular disease, stroke, thromboembolic disease, diabetes, bone fractures, cataracts, dementia, and developmental disorders.[8] Additionally, the financial costs of smoking to society are calculated to be over $300 billion per year.[8,21,22] As evidence grows in support of the magnitude of health impacts of smoking, we in the health profession are faced with a growing urgency to provide effective treatments for nicotine dependence. Historically, population-based smoking cessation treatment has involved major drives to inform the public of the harms of smoking. Today, allied health professions are uniformly trained to *ask* about smoking, *advise* smokers to quit, and *refer* to effective treatment.[23] Efforts such as these have resulted in a decrease in US smoking rates from 42.7% in 1964, at the time of the Surgeon General's first report, to 15.5% as of 2016.[8,11,24,25] However, with a decrease in smoking rates over the last 50 years, there has been a major shift in the characteristics of smokers who comprise the US smoking population

today. Today, smoking occurs primarily among people with low education, low income, and high rates of psychiatric and substance abuse disorders (approximately 40% of smokers have a mental illness).[8,26–28] In fact, those who do not complete high school are now 9 times more likely to smoke than those who complete high school.[26] Education, income, and mental illness are all significant barriers to successful smoking cessation treatment.[29–31] Today's smoker has a success rate for unassisted quit attempts of only 3-5%[32] and may require as many as 30 unassisted quit attempts before successfully quitting.[33] Together, the high morbidity and mortality of smoking, new barriers, and the low success rate of unassisted quit attempts, have created an ethical mandate within the healthcare field for more effective, evidence-based smoking cessation treatment.

4. Why the stated objectives of the research are important: Smoking cessation medications that are effective for reducing withdrawal in heavy smokers[34,35] have been relatively ineffective for treatment of light smokers.[7,36] The nicotine patch, a full agonist at the nicotinic acetylcholine receptor, reliably decreases nicotine withdrawal symptoms and reduces the frequency of smoking urges associated with smoking abstinence.[37] A study on light daily smokers (5-10 cigarettes per day) showed 6-month post-quit abstinence rates of 40% when taking varenicline vs. placebo (21%).[38] This study sample (those who smoke 5-10 cigarettes/day) represents the heaviest of the light and intermittent smoking category. At the higher end (e.g. 5-10 cigarettes per day) of the light smoking continuum, individuals are more likely to experience and respond to a medication that reduces withdrawal symptoms.[39] In summary, studies on pharmacologic treatment of LITS have shown very little success except for varenicline which has only been tested in LITS who use 5-10 cigarettes per day.

5. The rationale for performing this research: A novel approach to pharmacotherapy in LITS is targeting cue-based smoking through the use of varenicline. Varenicline has been found to decrease reward during cue exposure in humans[40] and studies have demonstrated that administration of varenicline decreases cue-based nicotine self-administration in low self-administering nicotine-dependent rats.[41,42] This suggests that a similar strategy might be successful in human light smokers.

2.3. DESIGN AND PROCEDURE

Treatment study: This study is designed to assess laboratory based and real world cue reactivity as well as smoking reduction and abstinence in LITS using varenicline vs. placebo over a 6-week period. The study design will be a 2-arm randomized, placebo-controlled trial on a sample of 12 light and intermittent smokers (LITS). Randomization groups will be to treatment with varenicline vs. placebo. This study will consist of a screening visit and the following 4 study visits:

Visit 1: Baseline - 4 weeks pre-TQD

Visit 2: 2 weeks pre-TQD

Visit 3: 1 pre-TQD

Visit 4: 2 post-TQD

The primary outcome will be cue reactivity measured in a laboratory setting, and in a real world setting through text-based response. Secondary outcomes will include smoking abstinence at 2-weeks post-TQD, smoking reduction across the 6-week study, and medication adherence and tolerance. The study will also provide exploratory assessments of moderators (individual variables, cue-based moderators, and smoking reward as a potential mediator. The study sample will consist of LITS (≤10 cigs/day) who smoke a minimum of 4 cigarettes per month and a maximum of 10 cigarettes per day. Participants will be randomized with 1:1 allocation to two arms (varenicline vs placebo), with 6 participants in each arm. Participants who pass screening will be randomized and receive study medication at their baseline visit (4 weeks

prior to the TQD). The following outline procedures for cue reactivity testing in a laboratory and real-world setting and testing of smoking abstinence and reduction:

Laboratory-Based Cue Reactivity: At each study visit, participants will be tested for cue reactivity in a lab-based paradigm. This will be assessed through a cue exposure test in which participants provide a report of their craving level after exposure to each block of images/pictures. They will also be exposed to smoking paraphernalia (lighters, cigarettes) prior to image blocks. More information can be found in section 6.5.

Real-word Cue Reactivity: Every day throughout the 6-week study period information will be collected through the following text-based situations: 1. Text "S" when they smoke a cigarette and answer several text-based questions, 2. Text "C" when they experience a craving and answer several text-based questions, and 3. At the end of the day (9:00PM), they will receive a text asking how many cigarettes they smoked that day and whether they took their morning and evening medications. See section 6.6 for more information and Appendix 22 for text message questions/prompts.

Behavioral treatment: At the baseline visit, all participants will receive 20 minutes of smoking cessation counseling including standard smoking cessation materials from the Quit at Duke Smoking Cessation Program.

Smoking Abstinence: 7-day point prevalence abstinence will be measured at the 2-weeks post-TQD study visit by self-report of not smoking for the last 7 days, a CO under 7 ppm, and salivary cotinine < 14 ng/ml.

Smoking reduction: Change in smoking from baseline to 2-weeks post-TQD will be assessed in 3 ways: 1. By self-report through daily text-based assessments of cigarettes per day and paper diaries, 2. By CO assessed at each study visit, and 3. Salivary cotinine assessed at each study visit.

Varenicline Extension: All participants who attend the final study visit (2-weeks post-TQD) will be offered an additional 6 weeks of varenicline. This will be provided to all participants regardless of their study allocation status. There are multiple reasons for this: 1. To provide evidence-based treatment to all participants, 2. To encourage those who might suspect they are on placebo to continue on until the final study visit, and 3. To provide a full 12 weeks of treatment for those who are on varenicline (standard of care). This will be up to the participants discretion and is not required.

Phone-based follow-up: Phone-based follow-up will occur at the below intervals:

> ***Call 1- After Baseline Visit:*** A phone follow-up will occur 2-5 days after the participant starts taking their medication to ensure that they are taking the medication correctly and to see if there are any initial side effects. A self-report of smoking (cigarettes/day) will also be collected. If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Call 2- 1-Week Post-TQD: A phone follow-up will occur 1 week after their TQD to ensure that they are taking the medications correctly, see if there are any side effects, and to assess self-report of smoking (cigarettes/day). If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

***Call 3- After Final Study Visit (No Varenicline Extension)*:** A phone follow-up will occur 2-5 days after the participant stops taking their medication to asses for any residual side effects. If there are side effects, a study medical provider will call them to follow-up and make any necessary recommendations. They will be asked to provide a self-report of smoking (cigarettes/day).

OR

Call 3- After Final Study Visit (Varenicline Extension): A phone follow-up will occur 2-5 day after the participant starts taking the medication to ensure that they are taking the medication correctly, to assess for any side effects, and to obtain a self-report of smoking (cigarettes/day). If side effects are reported, the study medical provider will call the participant and make necessary recommendations or dosage adjustments.

Call 4- 9-Week Follow-up Call (Varenicline Extension): A phone follow-up will occur at 5-weeks post-TQD (3 weeks after starting varenicline extension). This call will be to ensure that they are taking the medication correctly, assess for side effects, and obtain self-reported smoking (cigarettes/day). If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Call 5- After Varenicline Extension (Varenicline Extension): A phone follow-up will occur 2-5 days after the end of the 6-week varenicline extension period (8-weeks post- TQD) to see if they are any residual side effects from taking the medication. A self-report of smoking (cigarettes/day) will also be collected. If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

2.4. DURATION OF STUDY

Timeline (Table 1): The proposed study will be conducted over a 7-month period, with 2 months of preparation and 4 months for recruitment/study implementation, and 1 month to assess outcomes.

Table 1. Study Calendar	**6 months**		
	Stage 1 (2 months) Aug 15- October 15	**Stage 2** (3 months) Oct 15, 19 - January 1, 20	**Stage 3** (2 weeks) January 1-15 20
Staff Training			
IRB Approval/Database Build			
Recruitment + Enrollment			
Treatment			

Analyze Study Outcomes			

2.5. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

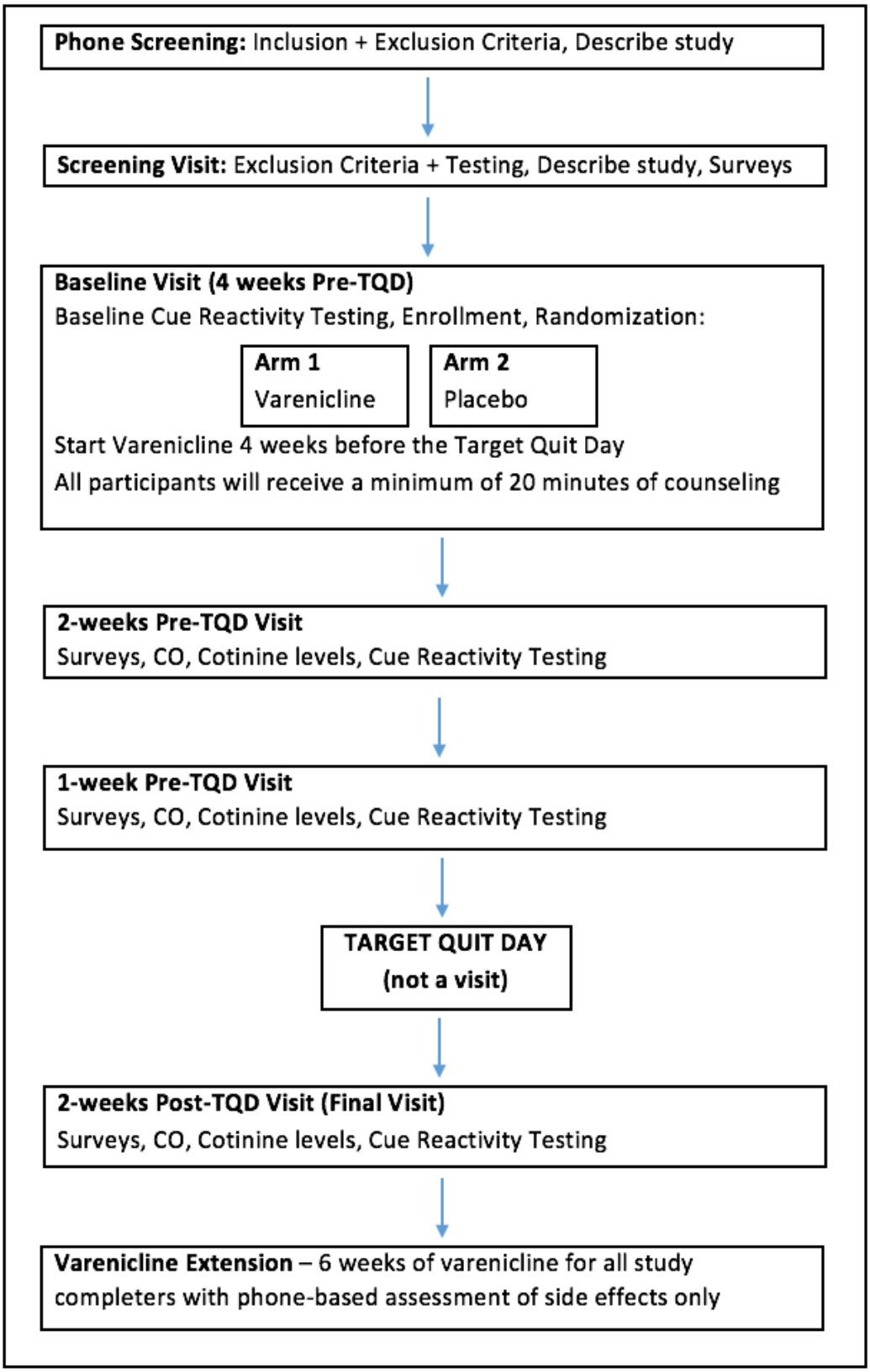
Statistical approach: general considerations. All analyses will follow an intent-to-treat approach with two-tailed tests and alpha = 0.05. Given repeated observations across multiple individuals and time points, many of the analyses in this study will be estimated by multilevel modeling (MLM) as implemented under mixed models.[43] MLM hierarchically organizes data as a function of person-specific variables and time-point specific variables. Unlike repeated-measures ANOVA, MLM is able to derive estimates with non-normal, including binary, distributions and unequal variances across time points and individuals, and, importantly, in the presence of missing values.[44,45] In addition to modeling between-person differences, MLM is also able to model within-person variables that change over time. Results will be described as means and standard deviations (or, medians and interquartile ranges if there are outliers or skewed data). Initially, for hypothesis testing, we will assess the distribution of the outcomes, and, if necessary, attempt to transform the response variable to bring about approximate normality of the distribution. In our initial analysis, we will test for a Group x Time interaction in the outcome.

Missing data. Because MLM procedures are based on maximum likelihood estimation and use all available data, MLM can accommodate missing data when the missing values are assumed to be missing at random.[44,45] Missing data will be examined to determine whether they can be defined as missing at random (MAR), which will give unbiased estimates of effect size. Often in smoking studies, missing values will be due to drop-out or other forms of treatment 'failure' which cannot be analyzed as MAR. To account for this, we will assume MAR to estimate group effects, to provide a conservative bound on effect size, but include missing values for drop-outs or other forms of treatment failure set to the worst response in the effect determination.

Power analysis. At a simple level, the primary comparison is the between group difference in change in the outcome. Assuming a level alpha (two-tailed) of 0.05, equal variances between the groups, then, at power of 80% and 90%, our design can detect a standardized difference (difference in mean/SD) in the change between the groups of 0.74 and 0.85 respectively. Effect sizes of this magnitude have been labeled as 'large' in the power analysis literature.[46] Because we are using techniques similar to Dr. Shiffman, we will refer to his study,[16] whose supplemental materials show in increase in craving after exposure to lab-based smoking cues in non-daily smokers from 16.49 (*SD*=15.13) to 19.19 (*SD*=16.10). If these estimates hold (SD=15.5), the between group difference detectable is 11.56 (=0.74*15.5). Use of the mixed model with interim data points, and control for baseline, should provide an estimated effect with smaller variance, and, hence, reduced effect size detectable, and greater power.

Secondary outcomes. Smoking behavior will be assessed via recent smoking CO breath testing, and saliva cotinine testing by comparing baseline measurements to later time points. This will allow us to determine whether there is a greater decrease in smoking in groups from each study group vs. control. These outcomes will be analyzed by mixed models to allow for change over time by person in the individual outcome. We have pre- specified these and other secondary outcomes to be analyzed, and at the project's end we will have a rich database to conduct other exploratory analyses. These outcomes are exploratory and correlative, and as such will not adjust for Type-I error in these analyses. Rather, any resulting publication will contain a statement of the exploratory nature of the findings, warn of the multiple testing issue, and note a requirement for replication.

3. STUDY SCHEMA



4. BACKGROUND AND SIGNIFICANCE

4.1. STUDY PURPOSE/RATIONALE

The overarching aim of this study is to improve our understanding response to varenicline among smokers who are driven to smoke primarily by conditioned cues rather than nicotine withdrawal. Heavy smokers appear to smoke due to nicotine withdrawal and also cues, whereas light and intermittent smokers (LITS) appear to smoke primarily due to cues.[1] Heavy smokers commonly experience nicotine withdrawal symptoms an hour or two after smoking each cigarette, smoke regularly throughout the day to avoid withdrawal symptoms.[2] On the other hand, light and intermittent smokers (≤10 cigarettes per day or on some days) typically do not experience nicotine withdrawal, and thus, primarily smoke in response to smoking cues (cue-based smoking).[3] The neurobiological basis of cue-based smoking is "cue reactivity"- a desire to smoke in response to smoking cues is initially learned by pairing smoking cues with smoking (nicotinic reward), and is maintained through repeated pairing of smoking cues and smoking.[4] A number of medications have been used to help LITS quit smoking but mostly none have not been successful.[5] One promising mechanistic pathways through which we may be able to decrease cue reactivity in LITS is nicotinic receptor antagonism - blocking nicotinic reward during smoking should decrease cue reactivity. Varenicline blocks nicotinic receptors and is known to decrease nicotinic reward.[6] Thus, in this study we will assess the effects of varenicline on changes in cue reactivity in LITS.

5. OBJECTIVES AND ENDPOINTS

	Objective	Endpoint	Analysis
Primary (1)	**Lab-Based Cue Reactivity:** To determine whether varenicline vs. placebo shows greater reduction in laboratory-based smoking cue reactivity.	This will be assessed over all study visits: (Baseline (4-weeks pre-quit), 2-weeks pre-quit, 1-week pre-quit and 2-weeks post-quit). Lab-based cue reactivity will be assessed at each visit through a paradigm in which the participant is presented with blocks of visual images and after each block is asked to provide a self-report of cigarette craving.	See Section 13.4
Secondary (2)	**Real-World Cue Reactivity:** To determine whether varenicline vs. placebo shows greater reduction of cue reactivity during "real-world" testing.	This will be assessed through daily text-based responses over the 6-week study period. Real world cue reactivity will be assessed each day through participant texting the study application. Participants will be asked to send a text after each cigarette they smoke, when they experience a craving, and at the end of each day.	See Section 13.5
Secondary (3)	**Smoking Abstinence:** To determine whether varenicline is more effective than placebo for achieving 7-day point prevalence smoking abstinence at the 2-weeks post-TQD day visit.	Abstinence will be defined as self-report of not smoking for the last 7 days, CO breath test < 7 ppm, and salivary cotinine under 14 ng/ml.	See Section 13.5
Secondary (4)	**Smoking Reduction:** To determine whether varenicline more effective than placebo for smoking reduction over the 4-week pre-TQD smoking period and over the 2 week post-TQD period.	Smoking reduction will be assessed in three ways: 1. Daily end-of-the-day text messages in which participants provide a self-report of how many cigarettes they smoked that day (in addition to paper self-report diaries), 2. CO breath testing at each study visit, and 3. Salivary cotinine testing at each study visit.	See Section 13.5
Secondary (5)	**Adherence:** To determine whether varenicline has acceptable adherence when compared to placebo in this population.	Medication adherence will be measured using daily text-based assessment of medication use and paper self-report diaries.	See Section 13.5

Secondary (6)	**Tolerability:** To determine tolerability through participant self-report.	Tolerability will be assessed through an open-ended question on potential self-effects asked at baseline and each study visit.	See Section 13.5
Exploratory (7)	**Baseline Variables (Moderator):** To determine whether a variety of baseline variables (age, gender, sex, race, nicotine dependence, anxiety, depression, stress, baseline smoking enjoyment) are associated with differential treatment response between varenicline and placebo described within objectives 1-4.	Baseline variables will be assessed through surveys conducted at baseline.	See Section 13.5
Exploratory (8)	**Cue Variables (Moderator):** To determine whether a variety of experiential or environmental variables (stress level, frustration, anger, sadness, boredom, positive affect, social interaction, time of day, familiar smoking place, smells, visual stimuli, alcohol use) are associated with our primary the intensity of cue reactivity for a particular cue and with smoking on a particular day.	Cue variables will be assessed through text based questions sent to participants. The frequency and intensity reported on these variables will also be assessed as treatment moderators – i.e. for their association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).	See Section 13.5
Exploratory (9)	**Adherence (Moderator):** To determine whether adherence to varenicline is associated with outcomes across multiple time points (2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD).	Medication adherence will be measured using a text-based questions and will be assessed for an association with objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).	See Section 13.5
Exploratory(10)	**Change in Reward (Mediators):** To determine whether changes (baseline to each time point) in physical smoking satisfaction, pleasure from smoking or other forms of "smoking reward" are associated with differential treatment response in objectives 1-4 (laboratory-based and real-world cue reactivity, smoking abstinence and reduction).	Smoking reward will be assessed at study visits through surveys designed to capture satisfaction, enjoyment, resolution of urge etc. related to smoking.	See Section 13.5

6. INVESTIGATIONAL PLAN

6.1. RECRUITMENT AND ENROLLMENT PROCEDURES:

Recruitment Sites: We plan to consent up to 30 participants and enroll/randomize 12 participants over a 3-month period. The study will take place at the Duke Center for Smoking Cessation.

General Recruitment Strategies: We will conduct general recruitment through social media advertising and paper flyering.

Recruitment through the Duke Smoking Cessation Program: The study will recruit through the Duke Smoking Cessation Program – a network of 12 specialized smoking cessation clinics each run by a Medical Provider and all overseen by Dr. Davis (Principal Investigator). All Duke Smoking Cessation Program providers are trained in on-going studies and assist in

the recruitment of patients into studies (if patients are interested in research studies). All patients who do not successfully quit smoking after participating in a study are rescheduled with a Duke Smoking Cessation Program provider. This study would employ the use of nine Duke Smoking Cessation Program clinics (Duke Primary Care [DPC] Oxford, DPC Croasdaile, Duke Family Medicine, Duke Outpatient Clinic, Duke Private Diagnostic Clinic [PDC] - South Durham, PDC Brier Creek, PDC Raleigh, Asthma, Allergy, and Airway Center, and Duke Employee and Occupational Health and Wellness). Anyone who is referred for a clinic visit will have his or her medical record reviewed for research study eligibility. If they meet the eligibility criteria, then a research staff member will contact them via phone or MyChart message to see if they are interested. If interested, they are phone screened or asked to complete a REDCap screening survey, and then potentially scheduled for a screening visit. Individuals that have opted out of research via the medical record will not be contacted.

Recruitment through the Duke Primary Care Research Consortium: Prior research conducted through our center has relied in part on the Duke Primary Care Research Consortium. This consortium oversees all research within Duke Primary Care: a network of over 30 clinics primarily around the Research Triangle Area. The consortium is primarily interested in whether studies offered to patients would provide safe and effective means for supporting or improving health outcomes. Duke Primary Care clinics serve a broad cross section of the community. Patients from the Duke Primary Care Research Consortium will be recruited from one of the 30 clinics. A study team member will conduct a query into the electronic health record through MaestroCare reports. After identifying individuals who fall within our recruitment categories, we will directly contact these patients by MyChart message and/or telephone to offer them additional information about the research study (Duke's Cold Call Policy).

6.2. STUDY/TREATMENT DURATION

The Target Quit Day (TQD) is defined as "Time Zero." There are 4 visits after the screening visit: Baseline (4-weeks pre-TQD), 2-weeks pre-TQD, 1-week pre-TQD, and 2-weeks post-TQD. Varenicline/placebo will begin 4 weeks prior to the TQD (at the baseline visit). Varenicline/placebo will continue for 2 weeks after the quit day. In total, participants will use study medication (placebo vs. varenicline) for 6 weeks. Participants who attend the final study visit (2-week post-TQD) will be offered an additional 6 weeks of varenicline (the varenicline extension). Phone-based follow up will occur at 3 time points: 2-5 days after baseline visit, 1 week after the TQD, and 2-5 days after the 2-week post-TQD visit. For those opting for the varenicline extension period, they will receive additional calls at 5-weeks post-TQD (3 weeks into the extension) and 2-5 days after the end of the varenicline extension period.

6.3. TREATMENT- MEDICATION

Double Blind Design: The study is double-blinded such that participants, research assistants, and study medical providers (each of whom have contact with participants) are unaware of group allocations. Pill bottles provided to participants will feature generic research labels (Medication X vs. Medication Z) through the pharmacy at Duke's Investigational Chemotherapy Services (ICS). The Clinical Research Coordinator (CRC), who oversees operations and has no contact with participants, will be aware of participant group allocation. **Varenicline Extension:** Participants who attend the 2-week post-TQD visit and opt to receive 6 additional weeks of varenicline will be provided with additional medications marked "varenicline" regardless of randomization status. Randomization status will not be broken prior to the varenicline extension.

Medication Distribution and Initiation: After randomization at the baseline visit, participants will be given one of the following medications based on allocation status: varenicline vs. placebo. Both medications will look the same. Medications and placebo will be given twice daily for a total of 6 weeks, with a ramp up period for the first week (see

Section 7). The first dose of medication will be given 4-weeks prior to the TQD. Participants will be provided with medication instructions (verbal and written), including the day on which they should start taking their medications. Participants will be asked to keep medication dispensing journals and smoking diaries. This will be confirmed/reviewed at subsequent study visits. Total length of medication use will be 6 weeks within the randomized protocol. **Varenicline Extension:** Participants who attend the 2-week post-TQD visit and opt to receive the additional 6 weeks of varenicline will receive medication marked "varenicline" regardless of randomization status. Randomization status will not be broken prior to the varenicline extension. Varenicline will be given twice daily for a total of 6 weeks, with a ramp up period during the first week of the varenicline extension period.

Packaging of Medications: See section 7.2.

6.4. BEHAVIORAL COUNSELING

Counseling: At the screening visit, participants will receive 20 minutes of smoking cessation counseling using evidence-based quit smoking methods and materials used in the Duke Smoking Cessation Program.[47] A review of instructions for the quit day, including having their last cigarette up to midnight the night prior to the quit day will be provided. Quit day preparation will include information on how to remove cigarettes from their house, and that abstaining from heavy alcohol or drug use is recommended. The counseling session will also include an exploration of individual motivations for quitting, reasons for relapse in the past, smoking triggers, and simple strategies for managing urges. A one-page handout will be provided, highlighting key points from the counseling session, and participants will be offered the Quit at Duke Smoking Cessation Program.

Reason for Brief Counseling: It is considered standard-of-care to receive evidence-based counseling together with pharmacotherapy.[47] For this study, counseling is administered at the Baseline visit to provide guidance for quitting smoking.

6.5. CUE REACTIVITY

Participants will sit in a comfortable chair in front of a computer screen and will be presented with series of images ("blocks") adapted from the International Affective Picture System (IAPS), a database of standardized images known to elicit attention, emotion, and smoking urges.[48,49] Image blocks will fall into four categories: A) Neutral; B) Proximal Smoking (e.g., cigarettes, ashtrays); C) Social Smoking (e.g., people smoking); and D) Unpleasant (e.g., crime scenes, disfiguring injuries). Neutral image blocks will serve as attentional controls to assess differential response from control images to smoking or affective images. Following each block, participants will be asked to provide ratings (0-10) of craving intensity. Blood pressure and heart rate will also be taken. Additionally, participants will also be exposed to in vivo cues by following instructions to touch/hold/smell smoking paraphernalia, including cigarettes, ashtrays, and lighters. There will be 3 blocks of 4 image sets presented, taking a total of 17 minutes.

6.6. TEXT-BASED ASSESSMENT

We will ask participants to interact with a text-based program **every day** throughout the 6-week study period. There will be three triggers for text-based interaction: 1. When the participant smokes a cigarette, they will send a text "s" to the text-based program, which will trigger a serious of questions, 2. When the participant feels craving to smoke a cigarette, they will send a text "c" to the text-based program, which will trigger a serious of questions, and 3. At the end of the

day, the program will send a question on number of cigs smoked that day and medication adherence. Samples of the text prompts/questions can be found in Appendix 22. Participants will be instructed not to text while driving and only to text when it is safe to do so. This is the same texting program approved for use in **Pro00089760.** Specifically, this protocol uses the same text-based questions, the same database format, the same operational program, and data safety measures, and is run by the same group of people for the same type of subjects (light smokers). If participants are noted to not be utilizing the text-based system, research study staff will call them via phone after 2 days of non-responsiveness.

7. STUDY DRUG- DOSAGES

The standard dose of varenicline is 1 mg BID[50] and is known to be well tolerated.

Varenicline or Placebo will be taken twice daily taken for 6 weeks, starting 4 weeks prior to the quit day and for 2 weeks after the quit day (6 weeks total).

Varenicline

The dose will be increased during week 1.

- Varenicline 0.5 mg, each morning x 3 days, then
- Varenicline 0.5 mg BID x 4 days, then
- Varenicline 1.0 mg BID x 5 weeks

Placebo:

Information on drug structure, formulation, and manufacturing will be provided by Central Compounding, and distributed by the Investigative Chemotherapy Services (ICS).

Varenicline Extension (for participants who attend the 2-week post-quit visit):

- Varenicline 0.5 mg, each morning x 3 days, then
- Varenicline 0.5 mg BID x 4 days, then
- Varenicline 1.0 mg BID x 5 weeks

7.1.1. DRUG MECHANISM OF ACTION

From FDA: "Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to α4β2 receptors. Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor."[50]

7.1.2. RATIONALE FOR USE OF STUDY DRUG IN THIS PARTICULAR SUPPORTIVE CARE CONTEXT

Rational for Design: A randomized controlled comparative design is important for this study because it establishes a comparison between each component and its comparator - varenicline vs. placebo.

7.2. PACKAGING AND LABELING

Blinded study drug(s) will be provided in bottles to the Investigational Chemotherapy Services (ICS) Pharmacy. All medications will be labeled according to Investigational Chemotherapy Service (ICS) Standard Operating Procedures to include at least: drug name/strength (with neutral language accounting for the blind/active-control), quantity, lot number, bottle number, expiration or retest date, IRB protocol number, and "for investigational use only." Placebo medications will be provided in non-descript packaging, similarly to non-placebo medications.

Investigational Chemotherapy Service - Duke Cancer Institute

(919) 668-0657

Patient: _____

Take 1 capsule, twice daily as directed (modified for ramp up period).

Varenicline 1mg OR Placebo (see dispensing schedule below)

Protocol number (Duke IRB PRO########)

Bottle # (unique number for tracking)

Dr. James Davis

Return bottles to pharmacy

Disp: Do not use after:_____

Caution: New Drug-Limited by Federal (United States) Law to Investigational Use Only

Medication Dispensing Schedule

Baseline Visit: Dispense 3 weeks of medication (varenicline vs. placebo): 1-week start up package (escalating dose) plus 2 weeks of continuation treatment (1 mg BID).

2-weeks pre-TQD Visit: Dispense 4 weeks of Medication (varenicline vs. placebo): 3 weeks of continuation treatment (1 mg BID) plus on additional week (1 mg BID; in case of rescheduling).

2-week post-TQD Visit: If requested, dispense 6 weeks of Varenicline: 1-week start up package (escalating dose) plus 5 weeks of continuation treatment (1 mg BID).

7.3. SUPPLY, RECEIPT, AND STORAGE

The Investigational Chemotherapy Services (ICS) Pharmacy will be responsible for receiving, storing, and inventorying the study drug(s) according to its Standard Operating Procedures.

7.4. DISPENSING AND PREPARATION

All study medications will be dispensed by the Investigational Chemotherapy Services (ICS) pharmacy. ICS will maintain detailed dispensation logs. Study staff will pick up medication orders prior to study visits. Once received, internal drug dispensation logs will be kept to ensure tracking of pill bottles.

7.5. DISPOSAL AND DESTRUCTION

Unused study drugs will be returned to the ICS for disposal/destruction.

7.6. DOSE MODIFICATION

If side effects from this drug are observed and determined to be minor, the medication dosing may be changed with the evening dose either moved earlier in the day or eliminated.

7.7. SAFETY CONSIDERATIONS

At each visit and follow-up phone call, we will also ask participants about the presence of side effects of any kind. If participants are found to have side effects of any kind, they will be recorded and will be assessed by the study medical provider to determine severity, whether it may have been caused by the drug, and whether it requires dose adjustment or discontinuation of the drug.

7.8. MISSED DOSES

Missed doses of medications will not be replaced. There will be no “catch up” for missed doses. We will capture data on missed doses through the medication adherence diary.

7.9. CONCOMITANT MEDICATIONS/THERAPIES

A medication list is provided for medications, which are contraindicated in the study (see Appendix 1). Participants will be asked to report the use of any new medications during the study. If new medications are started, the study medical provider will assess whether or not the participant must be removed from the study.

7.10. STUDY DRUG BLINDING

The study is double-blinded such that the participants, principal investigator, research assistants, and the study medical provider are unaware of group allocations. Pill bottles provided to participants will feature generic research labels (Medication X vs. Medication Z). Medications are dispensed by the ICS Pharmacy. The Clinical Research Coordinator

(CRC), who oversees operations and has no contact with participants, will be aware of participant group allocation. Emergency un-blinding procedures are in 11.3.

7.11. RANDOMIZATION

Prior to the study start date, a randomization list will be generated through the REDCap Randomization Module[51] for a sample of 12 with 1:1 allocation (6 in each arm) to varenicline vs. placebo via random permutation of integers without replacement.

7.12. RATIONALE FOR CORRELATIVE STUDIES

No correlative study will be performed.

7.13. DEFINITION OF EVALUABLE SUBJECTS, ON STUDY, AND END OF STUDY

This study defines a subject as evaluable if he or she competes the 2-week post-quit study visit.

7.14. EARLY STUDY TERMINATION

This study can be terminated at any time for any reason by the PI-sponsor. If this occurs, all subjects on study should be notified as soon as possible. Additional procedures and/or follow up should occur in accordance with Section 10.3, which describes the procedure for prematurely withdrawn patients.

8. SELECTION OF SUBJECTS: ELGIBILITY

Inclusion Criteria:

1. Age 18 years or above
2. Daily smoker using 10 or less cigarettes per day but a minimum of at least 1 cigarettes per week or 4 cigs/month.
3. Willing to quit smoking in the next 30 days
4. Is able to provide written informed consent (in English) to participate in the study and is able to read/understand the procedures and study requirements.
5. Is willing to voluntarily sign and date an informed consent form that is approved by an institutional review board before the conduct of any study procedure.
6. If female and of childbearing potential, is willing to use medically acceptable contraceptive measures for the duration of the study. Acceptable methods of contraception include (1) surgical sterilization (such as tubal ligation or hysterectomy, (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as rhythm method or Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.
7. Have access to a cell phone that can send and receive SMS text messages.

Exclusion Criteria:

1. Use of a smoking cessation medication (e.g. nicotine replacement, varenicline, bupropion) in last 7 days.
2. Current use of tobacco product other than cigarettes (e.g. e-cigarettes, smokeless tobacco) in the last 7 days
3. Score of 10 or greater on Patient Health Questionnaire (PHQ-9) Depression Scale[52,53]

4. Answer > 0 on suicidality question (Questions 9) of Patient Health Questionnaire (PHQ-9) Depression Scale[52,53]
5. Score of 15 or greater on the General Anxiety Disorder 7-item (GAD-7) Scale[54,55]
6. Active alcohol use disorder or hazardous drinking. This will be initially screened on the phone with the AUDIT-C[56,57], and a score 5 or greater is exclusionary for both men and women. Positive scores of 3 or 4 will result in study clinician assessment and discretion. At the in person-screening visit, the AUDIT[56,57] will be administered with scores of 8 or greater exclusionary.
7. Use of illicit drugs in the last month (marijuana, cocaine, opiates, benzodiazepines, and/or methamphetamine)
8. Severe symptomatic depression and or anxiety (study medical provider discretion)
9. Diagnosis of bipolar disorder, schizophrenia, PTSD and or adult ADHD (study medical provider discretion)
10. Chronic medical illness including diabetes with the use of insulin, Hemoglobin A1c > 7 (study medical provider discretion), heart disease diagnosed by angiogram, or COPD diagnosed by pulmonary function testing and requiring an oxygen supply
11. Specific medications (Appendix 1)
12. Abnormal finding on physical exam (study medical provider discretion)
13. Positive Urine Pregnancy Test (women of child bearing potential only; QuickVue Urine Pregnancy)[58]
14. Positive Urine Toxicology-5 Screen (methamphetamine, cocaine, opiates, benzodiazepines, THC)[59]
15. Unstable hypertension (Blood pressure > 160/100)
16. Renal failure with active or pending hemodialysis

Use of Inclusion/Exclusion Criteria: The primary considerations for the use of inclusion/exclusion criteria include consent (English, age), patient safety (illness, medications, blood tests, pregnancy), and generalizability (willingness to quit, cigarette use, drug and alcohol use, psychiatric illness).

Assessment and Follow-up of Specific Exclusion Criteria: If a participant is excluded based on criteria above, the study medical provider will further assess the exclusion through medical interview as needed. If this interview reveals a safety issue for the excluded individual, the medical provider will seek immediate medical assistance if necessary.

9. ASSESSMENTS AND PROCEDURES

9.1. OVERVIEW OF ASSESSMENTS

Medications will be continued for 6 weeks in each group with laboratory testing at (baseline (4-weeks pre-quit), 2-weeks pre-quit, 1-week pre-quit, and 2-weeks post-quit). The goal of study visits is to assess lab-based craving and to confirm the number of cigarettes smoked per day with objective confirmation via expired breath carbon monoxide (CO) and salivary cotinine. Follow-up phone calls will occur at 2-5 days after the baseline visit, 1-week post-TQD, and 2-5 days after the 2-week post-quit visit. For the varenicline extension period, additional phone follow-ups will occur at 5-weeks post-TQD (3 weeks into period) and 2-5 days after the varenicline extension period. The purpose of follow up phone calls is to assess side effects and self-reported cigarettes per day. Other assessments will be made through daily texts: Real world cue response, cigarettes per day and adherence to medications.

Assessment of smoking abstinence: Smoking abstinence will be tested at all study visits. A smoking diary will be used to assess self-reported cigarettes per day from the time of their last visit as well as real-time text data. At all visits, abstinence will be assessed by an expired air carbon monoxide (CO) breath test < 7ppm (96.0% sensitivity)[60–62] and salivary cotinine.

Efficacy assessments (smoking): Smoking abstinence will be tested at all assessment visits using self-report diaries and two forms of biochemical confirmation. Smoking diaries will be filled out every day with a request that the total number

of cigarettes smoked each day are entered and recorded by the participant in his or her diary. These will be reviewed at each study visit. Data from the real-time texting will also be used. At all visits, smoking status will be biochemically confirmed by a CO breath test and by salivary cotinine.

Medication adherence tracking: Medication use will be tracked through self-report paper diaries and text based questions – with one question on medication use per day. This will provide daily assessment of medication use adherence including number of pills taken and time of day pill was taken (morning vs evening).

Tolerance: Medication side effects will be assessed through a questionnaire provided at each study visit and at follow-up phone calls. To avoid "cueing" the patients on side effects (leading to over-reporting) participants will not be given a list of potential side effects with this questionnaire. Instead, they will be asked about side effects using open-ended question.

Management Findings Indicating Risk: Potential participants are screened for a number of factors/conditions including but not limited to suicidality, pregnancy (women of childbearing potential only), and other general health/mental health assessment measures that could indicate risk to the potential participant. All study findings from the screening visit are discussed with a study medical provider, who will provide evaluation, and if necessary will alert the participant's primary care provider or emergency services as needed.

Phone calls: Phone-based follow up will include questions on smoking, medication use, and side effects.

Table 2. Assessments	Screening Visit	Baseline Visit- 4-week pre-TQD (V1)	2-week Pre-TQD Visit (V2)	1-Week Pre-TQD Visit (V3)	TQD	2-week Post- TQD Visit (V4)
SCREENING TESTS						
1. Demographics/Contact Information	X					
2. Smoking History; Native/Converted, Daily/non-daily smoking	X					
3. Self-efficacy/motivation to quit (2 items)	X					
4. Patient Health Questionnaire (PHQ-9)	X					
4a. If positive PHQ-9, #9, C-SSRS Screener	X					
5. Generalized Anxiety Diagnosis (GAD-7)	X					
6. Alcohol Use Disorders Test (AUDIT, if applicable)	X					
7. Medical History + Medications	X					
8. Physical Exam and Review of Systems	X					
9. Urine Drug Screen	X					
10. Urine Pregnancy Test	X					
11. Minnesota Nicotine Withdrawal Symptoms Scale (MNWS)	X					
12. Fagerström Test for Nicotine Dependence (FTND)	X					
13. Positive and Negative Affect (PANAS)	X					
REPEATED TESTS						
1. Lab-Based Cue Reactivity Test		X	X	X		X
2. Center for Epidemiologic Studies Depression Scale (CES-D)		X	X	X		X
3. Perceived Stress Scale (PSS-4)		X	X	X		X
4. Recent Smoking Questionnaire		X	X	X		X
5. Mood and Physical Symptoms Scale (MPSS-2)		X	X	X		X
6. Cigarette Evaluation Questionnaire (MCEQ)		X	X	X		X
7. Smoking Urges (QSU, Brief 10-item)		X	X	X		X
8. Medication Side Effects Question		X	X	X		X
9. Salivary Cotinine		X	X	X		X
10. Carbon Monoxide Breath Test	X	X	X	X		X
11. Self-report Medication/Smoking Diary		X	X	X		X

*Citations for assessments can be found in section 9.5. Full assessments can be found in the Appendices.

9.2. SCREENING EXAMINATION

"Phone" Screening Procedures: The research study staff will conduct "phone screens" to verify that potential subjects fit the basic inclusion criteria for this particular study. These are traditionally done over the phone but may also be conducted in person or via the REDCap electronic survey. The research staff will be familiar with all IRB-approved study forms include the protocol, phone script, and phone screening questionnaire for the study. Each potential subject will be given a brief description of the study to assess eligibility and interest during the phone screen procedures. They will be asked to provide verbal consent for additional screening questions (to determine study eligibility). Every phone screen will be reviewed by a study medical provider to confirm eligibility prior to a participant coming for the screening visit. Preliminary contact information will be stored electronically in REDCap or in encrypted documents on secure servers, and any paper documentation is stored behind two locked doors. Research study staff will be responsible for scheduling screening visits, documenting pertinent information on the phone screen forms (for study medical provider review), and providing directions and appointment reminders for those potential participants meeting inclusion criteria. Each potential subject will be contacted via phone or email up to three times. If a subject is not reached after the maximum number of contact attempts, he/she will not be considered further for participation in the study unless the subject re-establishes contact. Screening appointments will be entered onto a shared the Outlook calendar (accessible to only study staff and identified by a phone screen ID number). Any changes to appointments, such as cancellations or requests to reschedule visits will be documented on the calendar. Those who pass the "phone screening" will be scheduled for an in-person screening visit.

Screening Visit Procedures: At the screening visit, participants are provided with the study Informed Consent Form by the Clinical Research Coordinator (CRC), and are given time to read over the document. They are provided the opportunity to ask the CRC any questions before signing the informed consent document. Once the Study Consent Form is signed, the potential participant will be provided with a copy of Duke's HIPAA Notice of Privacy Practices. Subject data to be collected at the screening visit includes: information on general demographics, general medical history including smoking history, vitals (height, weight, blood pressure, heart rate, and CO breath test), various assessments (see Table 2), a physical exam, a urine pregnancy test (for women of child-bearing potential), and urine drug screen. The study medical provider will perform the physical examination. The study medical provider will also provide 20 minutes of smoking cessation behavioral counseling. The screening visit will last approximately 120 minutes (2 hours).

If individuals score >0 on the PHQ-9, question 9, they will be administered the Columbia-Suicide Severity Rating Scale (C-SSRS) by study medical provider to determine eligibility. In case of severe emergency, EMS will be called. If individuals score higher than the cutoff for the AUDIT-C (administered via phone screen), then they may be asked to complete the full Alcohol Use Disorders Test (AUDIT) to determine study eligibility as it pertains to alcohol use.

If an individual is not interested in the study or screens out at any point, he or she will be referred to alternative treatment services.

If the participant passes all the screening criteria, they can be either scheduled for their baseline visit or continue directly into their baseline visit on the same day.

Participants will also be provided with daily self-report journals to document recent smoking, medication adherence, urges/withdrawal, and side effects. They will be asked to return these at the next study visit (completed).

9.3. TREATMENT PERIOD

Treatment Visits:
Visit 1: Baseline Visit (4-weeks pre-TQD; described above)

Visit 2: 2-weeks pre-TQD
Visit 3: 1-week pre-TQD

Visit 4: 2-weeks post-TQD

Visit 1: Baseline visit- 4-weeks pre-TQD: For convenience, this visit may be provided on the same day as the screening visit or on a different day in order to accommodate the participant's schedule. During the baseline visit, the participant will undergo randomization and initiate treatment with either varenicline vs. placebo. The participant and research study staff (including medical provider) will not know which group they are assigned as they will be labeled as Group 1 or Group 2. Medication instructions will be provided, including how and when to take medications.

Participants will be provided with 3 weeks worth of medications. There will be 1 weeks worth of the ramp up dose (0.5) mg and then 2 weeks worth of the full dose (1 mg BID).

Participants will be asked to complete the lab-based cue reactivity test as well as complete additional self-report assessments of mood and smoking (see Table 2). They will also provide a saliva sample for salivary cotinine, complete a CO breath test, and have their vitals assessed.

They will be signed up for the text-based program and provided with an instruction booklet on what to expect from the texting component of the program.

Participants will also be provided with daily self-report journals to document recent smoking, medication adherence, urges/withdrawal, and side effects. They will be asked to return these at the next study visit (completed).

Visit 2-4: At each visit, participants will complete tests/assessments (see Table 2). Participants will also complete an expired CO breath test, salivary cotinine testing, and have their blood pressure, heart rate, and weight measured. Self-report diaries on medication adherence, smoking, urge/withdrawal and side effects will be reviewed and confirmed for accuracy. Participants will receive 4 weeks' worth of new study medications at the 2-weeks pre-TQD visit (V2). This, in combination with their previous mediations) will allow them 7 weeks' worth of medication (6 weeks on treatment and 1 week buffer if they need to reschedule. Participants who attend the 2-weeks post-TQD (V4) will be offered 6 additional weeks of varenicline.

Phone follow-up: Phone follow-up will occur at the below intervals:

Call 1- After Baseline Visit: A phone follow-up will occur 2-5 days after the participant starts taking their medication to ensure that they are taking the medication correctly and to see if there are any initial side effects.

A self-report of smoking (cigarettes/day) will also be collected. If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Call 2- 1-Week Post-TQD: A phone follow-up will occur 1 week after their TQD to ensure that they are taking the medications correctly, see if there are any side effects, and to assess self-report of smoking (cigarettes/day). If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Call 3- After Final Study Visit (No Varenicline Extension)**:** A phone follow-up will occur 2-5 days after the participant stops taking their medication to asses for any residual side effects. If there are side effects, a study medical provider will call them to follow-up and make any necessary recommendations. They will be asked to provide a self-report of smoking (cigarettes/day).

OR

Call 3- After Final Study Visit (Varenicline Extension): A phone follow-up will occur 2-5 day after the participant starts taking the medication to ensure that they are taking the medication correctly, to assess for any side effects, and to obtain a self-report of smoking (cigarettes/day). If side effects are reported, the study medical provider will call the participant and make necessary recommendations or dosage adjustments.

Call 4- 9-Week Follow-up Call (Varenicline Extension): A phone follow-up will occur at 5-weeks post-TQD (3 weeks after starting varenicline extension). This call will be to ensure that they are taking the medication correctly, assess for side effects, and obtain self-reported smoking (cigarettes/day). If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Call 5- After Varenicline Extension (Varenicline Extension): A phone follow-up will occur 2-5 days after the end of the 6-week varenicline extension period (8-weeks post- TQD) to see if they are any residual side effects from taking the medication. A self-report of smoking (cigarettes/day) will also be collected. If there are side effects, a study medical provider will call them to follow-up and make any necessary dosage changes.

Questions to be asked at the above phone follow-ups can be found in Appendix 21.

9.4. COMPENSATION

Participant Compensation: Participants will receive the following compensation:

Visit 1: Baseline Visit (4-weeks pre-TQD) = $50

Visit 2: 2-weeks Pre-TQD Visit = $50

Visit 3: 1-week Pre-TQD Visit = $75

Visit 4: 2-weeks Post-TQD Visit = $100

Completion of 75% of all text messages for the week will provide $25/week Total = $150

Total compensation = $425

Use of ClinCards for compensation: Compensation will utilize Greenphire Inc. ClinCards,[63] which allows for electronic upload of funds to a "cash withdrawal card" provided to each participant. The Study Coordinator or Clinical Research Specialist will provide each participant with a ClinCard at the screening visit and will add the compensation to the card. After approval, the participant will have the money loaded onto the card within 3-5 business days.

9.5. STUDY ASSESSMENTS

9.5.1. DEMOGRAPHICS/CONTACT INFO

Demographic/contact information will be collected at the screening visit. This can be found in Appendix 2.

9.5.2. SMOKING HISTORY

At the screening visit, the subject will complete the Smoking History questionnaire (Appendix 3). This non-standardized questionnaire that provides information on the number of pack years, social support, additional tobacco product use, and other drug use.

9.5.3. SELF-EFFICACY/MOTIVATION

At the screening visit, the participant will complete 2 questions asking about confidence and motivation to quit. These can be found in Appendix 4.

9.5.4. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)[64,65]

The Patient Health Questionnaire PHQ-9 for Depression (Appendix 5) will be used to screen for current (within 2 weeks) depression at the screening visit. Participants who have scores of zero or higher on question 9 (suicidality) will be administered the C-SSRS and eligibility will be determined by the study medical provider. Patients with severe and symptomatic depression may also be excluded based on study medical provider discretion.

9.5.5. COLUMBIA-SUICIDE SEVERITY RATING SCALE-SCREENER (C-SSRS)[64]

The Columbia Suicide Severity Rating Scale-Screener (C-SSRS) is a questionnaire used for suicide assessment. It assesses suicidal ideation, intensity of ideation, and suicidal behavior. If the participant scores positive on question 9 of the PHQ-9, then the C-SSRS-Screener will be administered and reviewed by a study provider. The C-SSRS can be found in Appendix 6.

9.5.6. GENERALIZED ANXIETY DISORDER (GAD-7)[54,55]

Anxiety will be assessed using the GAD-7 (Appendix 7) at the Screening visit. The measure will be used to exclude participants from the study who have severe symptomatic anxiety based on study medical provider discretion.

9.5.7. ALCOHOL USE DISORDERS TEST (AUDIT)[67,68]

The AUDIT (full) is a 10-item questionnaire used to screen people for alcohol use. This will only be administered at the Screening visit if the potential participant scored higher than the cutoff scores on the AUDIT-C (on phone screen) and meets all other eligibility criteria. This can be found in Appendix 8.

9.5.8. MEDICAL HISTORY

Medical history assessments will be completed by each subject. This assessment will include questions about any significant medical diagnoses, recent hospitalizations, surgeries, family history, social history, and medication use. Appendix 9 provides an overview of medical history information to be collected and is considered a baseline measure.

9.5.9. PHYSICAL EXAM/REVIEW OF SYSTEMS

At the Screening visit, a study medical provider will conduct a physical exam of the participant for general health. Abnormal findings during the exam can be used to exclude participants from the study. They study medical provider will also discuss the review of systems (ROS), which is a list of possible symptoms covering the organ systems. These can be found in Appendix 10.

9.5.10. MINNESOTA NICOTINE WITHDRAWAL SCALE (MNWS)[65]

The Minnesota Nicotine Withdrawal Symptoms Scale (MNWS) is a 15-item scale that is designed to measure nicotine withdrawal symptoms (i.e. craving, irritability, anxiety, difficulty concentrating, restlessness, increased appetite or weight gain, depression, and insomnia). The MNWS will be administered at the screening visit. The complete MNWS can be found in Appendix 11.

9.5.11. FAGERSTROM TEST FOR NICOTINE DEPENDENCE (FTND)[66]

The FTND (Appendix 12) is a validated measure consisting of 6 items that assess a participant's level of physical nicotine dependence. The FTND will be administered the screening visit.

9.5.12. POSITIVE AND NEGATIVE AFFECT SCHEDULE (PANAS)[67]

The PANAS is a self-report questionnaire consisting of two 10-item scales measuring both positive and negative affect as personality traits. This can be found in Appendix 13.

9.5.13. CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE (CES-D)[68]

The Center for Epidemiologic Studies Depression Scale (CES-D) is a 20-item scale that asks participants to rate how often they have had symptoms of depression (following the DSM-V). The scale will be administered at all 4 study visits. The complete CES-D can be found in Appendix 14.

9.5.14. PERCEIVED STRESS SCALE (PSS-4)[69,70]

The Perceived Stress Scale (PSS-4) is a 4-item used to measure the perception of stress. Higher PSS scores have been associated with lower rates of smoking cessation. The scale will be administered at all 4 study visits and can be found in Appendix 15.

9.5.15. RECENT SMOKING QUESTIONNAIRE

At all in-person study visits, a participant's recent smoking habits will be assessed using the Recent Smoking Questionnaire (Appendix 16). This non-standardized, 4-item questionnaire provides information about the participants smoking behavior over the last 7 days.

9.5.16. MOOD AND PHYSICAL SYMPTOMS SCALE (MPSS-2)[71]

The Mood and Physical Symptoms Scale is a two-question scale to assess urges to smoke over a 24-hour period. It will be administered at all 4 study visits. The MPSS-2 can be found in Appendix 17.

9.5.17. MODIFIED CIGARETTE EVALUATION QUESTIONNAIRE (MCEQ)[72]

The Modified Cigarette Evaluation Questionnaire (mCEQ) is a 12-item survey that assesses the rewarding and aversive effects of smoking. It will be administered at all 4 study visits. The mCEQ can be found in Appendix 18.

9.5.18. QUESTIONNAIRE OF SMOKING URGES (QSU-BRIEF)[73,74]

The Questionnaire of Smoking Urges (QSU) is a 10-item survey to assess smoking cravings and urges. This will be administered at all 4 study visits and can be found in Appendix 19.

9.5.19. SMOKING AND MEDICATION USE[75,76]

Participants will be given a diary that will assess their cigarette use and medication adherence throughout the study. The diary will be given at screening visit and will be collected and reviewed at all study visits. Any omissions will be reviewed with the participant by study staff and every effort will be made to obtain accurate and complete diary data. The combined smoking, medication use, and urge/mood withdrawal diary can be found in Appendix 20.

9.5.20. MEDICATION SIDE EFFECTS QUESTIONNAIRE

Participants will be asked about any medication side effects they have been experiencing at all 4 study visits. Of self-reported side effects, they will be asked to rate the severity of the side effect (1- not at all severe to 7-extremely severe) as well as its frequency (From "Just once" to "More than once a day"). The research study staff as well as the study

medical provider will review this form. If a side effect has a severity of 3 or greater, they require follow-up from the PA. Severity scores of 1-2 are considered mild, 3-5 are considered moderate, and 6-7 are considered severe. An example of the Medication Side Effects Questionnaire can be found in Appendix 21.

9.5.21. TEXT-BASED MESSAGING

During the text messaging period, participants will be asked to text when they smoke and when they have, which will trigger additional questions. They will also be asked about overall cigarettes smoked that day as well as medication adherence. Examples of questions can be found in Appendix 22.

9.5.22. EXHALED CARBON MONOXIDE BREATH TEST[60–62]

The Exhaled Carbon Monoxide Breath Test will be used as objective confirmation of participant-reported number of cigarettes smoked per day. Exhaled Carbon Monoxide Breath testing will be evaluated at all in-person follow-up visits. Values less than 7 ppm are considered abstinent (96.0% sensitivity and 93.3% specificity).

9.5.23. SALIVARY COTININE

The salivary cotinine test is sensitive and specific for smoking cessation (95.0% sensitivity and 97.0% specificity). Cotinine has a 20-hour half-life and as such is useful for identification of tobacco use several days after smoking.[77]

10. END OF TREATMENT

The 2-week post-TQD visit, will be the end of randomized treatment. Participants who choose to continue treatment may request the varenicline extension and receive 6 additional weeks of varenicline at this point.

10.1. FOLLOW-UP PERIOD

If participants do not complete the varenicline extension period, they will receive one final phone call 2-5 days after their 2-weeks post-TQD study visit. They will be asked about any lingering side effects and self-report smoking (cigarettes per day). Any reported side effects will be reported to the study medical provider, who will follow-up with the participant and make any necessary recommendations.

If participants opt to complete the 6 additional weeks of varenicline, they will receive one final phone call 2-5 days after the varenicline extension period. They will be asked about any lingering side effects and self-report smoking (cigarettes per day). Any reported side effects will be reported to the study medical provider, who will follow-up with the participant and make any necessary recommendations.

10.2. END OF STUDY

Study participation will end with the 2-week post-TQD visit, unless a participant chooses to receive the varenicline extension. If the latter, then they will continue on for an additional 6 weeks of varenicline treatment. If participants express interest in continued smoking cessation services, a referral will be made to the Duke Smoking Cessation Program

or other resources for further support. After all participants have completed the study, the study data collection period will be considered over, and the team will begin analysis of results.

10.3. EARLY WITHDRAWAL OF SUBJECT(S)

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Patient Compliance
- Protocol deviation
- Administrative issues
- Disease progression
- Pregnancy

10.3.1. FOLLOW-UP REQUIREMENTS FOR EARLY WITHDRAWAL

If a participant has cause for premature withdrawal, or if the PI decides that the participant should withdraw, he or she will be asked to return all medications and no further medications will be dispensed.

10.3.2. REPLACEMENT OF EARLY WITHDRAWAL(S)

We will not replace participants who drop out of the study.

11. SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events and serious adverse events, as defined below. At each study visit, the PI or study staff must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

11.1. ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject receiving study therapy and which does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study therapy that may or may not be related to use of the study therapy. From the time the subject is randomized through the End of Study visit (as defined in Section 10), all AEs must be recorded in the side effect case report form (located on REDCap).

AEs will only be assessed according to the CTCAE version 4.0 if required for a monitoring visit/audit. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), or severe (3). Any AE's that are considered life-threatening (4) or fatal (5) will be reported according to the Serious Adverse Event reporting (see section 11.2).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study therapy
- Probably: The AE is likely related to the study therapy
- Possible: The AE may be related to the study therapy
- Unlikely: The AE is doubtfully related to the study therapy
- Unrelated: The AE is clearly NOT related to the study therapy

Any AE's reported by participants as having a severity of 3 or greater (on a scale of 1-7) will require study medical provider review/follow-up. AE's are considered mild if they have a severity of 1-2, moderate if they have a severity of 3-5, and severe if they have a severity of 6-7.

11.1.1. AES OF SPECIAL INTEREST

Adverse Events related to Varenicline used in prior studies have been minimal and no SAEs have occurred. As such there are no adverse events that will require special attention.

11.1.2. REPORTING OF AES

During each annual IRB review of the protocol, a list of all AEs will be provided to the IRB for review. This report includes whether the AE was likely related to study procedures, whether it impacted subject participation, whether the AE was resolved, and any other action taken.

11.2. SERIOUS ADVERSE EVENTS

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life-threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions

11.2.1. REPORTING OF SAES

Life-threatening (grade 4 or 5) SAEs, deaths, and unknown reactions or unexpected events that occur in the course of any patient's treatment of study (from the time of consent) or within 30 days following cessation of treatment are reportable. SAEs will be submitted to the IRB per standard protocol. The initial report for each SAE or death should include <u>at minimum</u> the following information:

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred

- Description of SAE
- Description of patient's condition
- Indication whether the patient remains of study
- Causality or causal relationship

De-identified source documentation (i.e. physician study notes) must be sent with the SAE Report Form. Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke IRB as soon as possible using the same forms mentioned above.

As soon as an investigator becomes aware of an AE that meets the definition of serious:

- The Study Coordinator will submit to IRB or designee within 24 hours of Investigator's awareness, even if it is not felt to be drug related.

SAEs will be reported by the PI in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office, NIDA, and FDA.

SAEs will be reported to the DUHS IRB using the following timelines:

- 24 hours – for an unanticipated study-related death
- 1 week (5 business days) – for an unanticipated problem that is a serious adverse event
- 2 weeks (10 business days) – for an unanticipated problem that does not meet the criteria of a serious adverse event

In accordance with applicable regulations, investigators will submit the SAE report to their local IRB according to local IRB institutional guidelines. Dr. Davis, the study PI is responsible for reporting the serious adverse event to the FDA in accordance with 21 CFR 312.32. Any SAE that is possibly related and unexpected will be reported to the FDA no later than 15 calendar days upon notification of the event. The FDA will be notified of any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after notification. This will be done by the study coordinator.

- These reports are to be filed utilizing the Form FDA 3500A (MedWatch Form) completed by the study coordinator/DCI.

11.3. EMERGENCY UN-BLINDING OF INVESTIGATIONAL TREATMENT

The Clinical Research Coordinator, Sr. will not be blinded to the treatment. The Principle Investigator as well as the Clinical Research Specialist, other Clinical Research Coordinator, study medical provider, and statistician will be blinded. In the case that Emergency un-blinding is required, the Principle Investigator will contact the Clinical Research Coordinator, Sr. directly to obtain the necessary information. Emergency contact information for un-blinding will be the email and cell phone number of Jillian Dirkes, jillian.dirkes@duke.edu, 423-833-4376.

11.4. OTHER REPORTABLE INFORMATION

Other reportable information including pregnancy, development of disease, or hospitalization for non-study related causes will be reported as AEs or SAEs depending on the severity and assessed as to whether these are related to study procedures.

11.5. SPECIAL WARNINGS AND PRECAUTIONS

There are no special warnings or precautions for this study.

11.6. STOPPING RULES

The study will be stopped prior to its completion if: **1**. difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; **2**. any new information becomes available during the study that necessitates stopping the study; **3**. there are significant treatment related toxicities that become evident through the course of the study (e.g. severe and repetitive unanticipated side effects or death); or **4**. other situations occur that might warrant stopping the study. Emergency unblinding procedures can be found in section 11.3. Determination of breaking the blind will be up to the principal investigator.

11.7. SAFETY OVERSIGHT COMMITTEE (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities, and new information that may affect subject safety or efficacy. Annual safety reviews include but may not be limited to review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analysis as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see Section 12 for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator greater-than-minimal-risk intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standing operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements. The DCI Safety Oversight Committee (SOC) will perform annual reviews on findings from the DCI Monitoring Team visit and additional safety and toxicity data submitted by the Principal Investigator.

11.8. EXTERNAL DATA AND SAFETY MONITORING BOARD (DSMB)

DSMBs are usually advised for Phase III multi-center clinical trials in which study participants are exposed to substantial risk or vulnerable populations are studied. This study, however, will be conducted at only one study site in Durham, North Carolina. Based on extensive clinical experience with varenicline, there is no reason to expect significant risks to subjects. Additionally, vulnerable populations will not be studied in this protocol. Hence, we have concluded that oversight by the scientific and medical team will be adequate for this study and that a formal DSMB will not be needed.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING

This clinical research study will be monitored both internally by the PI and institutionally by the Duke Cancer Institute (DCI). In terms of internal review, the PI will continuously monitor and tabulate adverse events. Appropriate reporting to the Duke University Medical Center IRB will be made. If an unexpected frequency of Grade III or IV events occur, depending on their nature, action appropriate to the nature and frequency of these adverse events will be taken. This

may require a protocol amendment, dose de-escalation, or potentially closure of the study. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled;
- Stopping rules for toxicity and/or response are met;
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of AEs and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.
- DCI review and monitoring of this protocol occurs in accordance with the NCI-approved Data and Safety Monitoring Plan.

Briefly, protocol review begins with an initial review by the Cancer Protocol Committee (CPC), which assesses the ethics and safety of the protocol. Documentation of these assessments will be maintained. Formal, independent monitoring will be conducted by the DCI Monitoring Team after the first 3 subjects are enrolled, followed by annual monitoring of 1-3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk. DCI Monitoring Team reports and additional data/safety/toxicity reports submitted by the PI will be reviewed by the Safety Oversight Committee (SOC) on an annual basis. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. Monitoring visits may also be initiated upon request by DUHS and DCI Leadership, CPC, SOC, a sponsor, an investigator, or the IRB.

A senior study staff member based at the Center for Smoking Cessation in Durham will be responsible for monitoring each site at least quarterly. This monitoring will include review of all consent forms completed since the previous monitoring visit, 3-5 case report forms (or more if deemed necessary), any on-site regulatory documentation, and training documentation for site study staff.

12.2. AUDITS

The Duke School of Medicine Clinical Trials Quality Assurance (CTQA) office may conduct confidential audits to evaluate compliance with the protocol and the principles of GCP. The PI agrees to allow the CTQA auditor(s) direct access to all relevant documents and to allocate his/her time and the time of the study team to the CTQA auditor(s) in order to discuss findings and any relevant issues.

CTQA audits are designed to protect the rights and well-being of human research subjects. CTQA audits may be routine or directed (for cause). Routine audits are selected based upon risk metrics generally geared towards high subject enrollment, studies with limited oversight or monitoring, Investigator-initiated Investigational Drugs or Devices, federally-funded studies, high degree of risk (based upon adverse events, type of study, or vulnerable populations), Phase I studies, or studies that involve Medicare populations. Directed audits occur at the directive of the IRB or an authorized Institutional Official.

CTQA audits examine research studies/clinical trials methodology, processes, and systems to assess whether the research is conducted according to the protocol approved by the DUHS IRB. The primary purpose of the audit/review is to verify that the standards for safety of human subjects in clinical trials and the quality of data produced by the clinical trial research are met. The audit/review will serve as a quality assurance measure, internal to the institution. Additional

goals of such audits are to detect both random and systemic errors occurring during the conduct of clinical research and to emphasize “best practices” in the research/clinical trials environment.

12.3. DATA MANAGEMENT AND PROCESSING

12.3.1. CASE REPORT FORMS (CRFS)

The electronic and paper CRF will be the primary data collection document for the study. The CRFs will be updated in a timely manner following acquisition of new source data. Only approved study staff including the PI, PA, and CRS are permitted to make entries, changes, or corrections in the CRF.

Errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The PI or authorized key personnel will maintain a record of the changes and corrections.

An audit trail will be maintained automatically by the electronic CRF management system REDCap.[78] Designated personnel will complete user training, as required or appropriate per regulations.

12.3.2. DATA MANAGEMENT PROCEDURES AND DATA VERIFICATION

Designated personnel using the electronic CRF will have access based on their specific roles in the protocol. The PI, PA, and CRS will have access.

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, the CRC will cross-reference the data to verify accuracy. Missing or implausible data will be highlighted for the PI requiring appropriate responses (i.e. confirmation of data, correction of data, completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

12.3.3. STUDY CLOSURE

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories

13. STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

13.1. ANALYSIS SETS

Dataset will be collected through the 12 week post quit follow-up visit. Data will include information from test/assessment, self-report diaries, and objective tests of urine, saliva, and expired CO. All data measures will be captured using REDCap,[78] an encrypted, HIPAA compliant, data collection system. Data entry is time-stamped for use in calendar-based assessment visits with capacity for upload into statistical programs Excel, Statview, SAS, SPSS, MPlus, and R. Trained Duke staff will conduct data integrity processes for REDCap data.[78]

13.2. PATIENT DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Participants will be adult smokers recruited through the Duke Center for Smoking Cessation.

13.3. TREATMENTS

Study Drug: Varenicline (1mg) vs. Placebo

13.4. PRIMARY OBJECTIVE

Varenicline vs. placebo will demonstrate greater reduction in cue reactivity.

13.4.1. VARIABLES

Cue reactivity, cigarettes smoked per day, expired CO, and salivary cotinine

13.4.2. STATISTICAL HYPOTHESIS, MODEL, AND METHOD OF ANALYSIS

Statistical approach: general considerations. All analyses will follow an intent-to-treat approach with two-tailed tests and alpha = 0.05. Given repeated observations across multiple individuals and time points, many of the analyses in this study will be estimated by multilevel modeling (MLM) as implemented under mixed models.[43,45,79] MLM hierarchically organizes data as a function of person-specific variables and time-point specific variables. Unlike repeated-measures ANOVA, MLM is able to derive estimates with non-normal, including binary, distributions and unequal variances across time points and individuals, and, importantly, in the presence of missing values. In addition to modeling between-person differences, MLM is also able to model within-person variables that change over time. Results will be described as means and standard deviations (or, medians and interquartile ranges if there are outliers or skewed data). Initially, for hypothesis testing, we will assess the distribution of the outcomes, and, if necessary, attempt to transform the response variable to bring about approximate normality of the distribution. In our initial analysis, we will test for a Group x Time interaction in the outcome. If non-significant, we will test a main effects model, including Group and Time. To allow for

correlations between observations, an unstructured correlation structure will be assumed. While the two groups should be equal at baseline due to randomization, in our analyses, the outcome will be estimated as changes from baseline. In compliance with recommendations from the Joint Commission, we will control for baseline. For each study, we have specified a primary outcome (cue reactivity), and thus will not need to adjust an overall Type-I error rate for multiple testing (e.g. Bonferroni Correction[80,81]) of primary outcomes.

13.4.3. HANDLING OF MISSING VALUES, CENSORING, AND DISCONTINUATIONS

Missing data. Because MLM procedures are based on maximum likelihood estimation and use all available data, MLM can accommodate missing data when the missing values are assumed to be missing at random.[86,91] Missing data will be examined to determine whether they can be defined as missing at random (MAR), which will give unbiased estimates of effect size. Often in smoking studies, missing values will be due to drop-out or other forms of treatment 'failure' which cannot be analyzed as MAR. To account for this, we will assume MAR to estimate group effects, to provide a conservative bound on effect size, but include missing values for drop-outs or other forms of treatment failure set to the worst response in the effect determination.

13.5. SECONDARY OBJECTIVES

Secondary outcomes. Physiologic arousal will be assessed during cue reactivity testing via skin conductance, heart rate, and blood pressure measurements. Physiologic outcomes will be used as a correlate of self- reported craving in response to visual cues. Smoking behavior will be assessed via smoking diaries, CO testing, and cotinine testing comparing baseline measurements to later time points to determine whether there is a greater decrease in smoking in groups from each study group vs. control. These outcomes will be analyzed by mixed models to allow for change over time by person in the individual outcome. We have pre- specified these and other secondary outcomes to be analyzed, and at the project's end we will have a rich data base to conduct other exploratory analyses. These outcomes are exploratory and correlative, and as such will not adjust for Type-I error in these analyses. Rather, any resulting publication will contain a statement of the exploratory nature of the findings, warn of the multiple testing issue, and note a requirement for replication.

Treatment of covariates and potential moderators. We will assess baseline variables for association with cue response and smoking behavior outcomes. Baseline variables assessed will include age, gender, race, education, baseline nicotine dependence, stress, anxiety, depression, self-efficacy, and nicotine metabolic rate. If a baseline variable is found to be associated with change in cue reactivity or smoking behavior, it will be treated as a covariate in a secondary analysis and assessed as a potential moderator of treatment effect.

13.6. SAMPLE SIZE ESTIMATION

Sample size estimation based on margin of error

Power analysis. As a pilot study, statistical power will be minimal due the small sample size.

13.7. EXPLORATORY OBJECTIVES

Objectives 7-10 are all exploratory. These are analysis of moderation and mediation and are underpowered to show statistical significance. They are provided to help guide future study.

13.7.1. KEY EXPLORATORY OBJECTIVE

Not applicable.

13.7.2. OTHER EXPLORATORY OBJECTIVES

Not applicable.

13.8. INTERIM ANALYSES

This study is being conducted in order to provide preliminary evidence for a P01 grant proposal on light smokers that will be submitted on January 25, 2020. Regardless of our progress in this study, we will conduct an interim analysis in late December or early January in order to provide results for this grant proposal. The blind will be broken for this analysis. An additional interim analysis may be conducted near the time of the grant review if additional data is deemed helpful for grant review.

14. ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

14.1. REGULATORY AND ETHICAL COMPLIANCE

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

14.2. DUHS INSTITUTIONAL REVIEW BOARD AND DCI CANCER PROTOCOL COMMITTEE

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e. amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within one year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within one year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

14.3. INFORMED CONSENT

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject. The Principal Investigator is responsible for asking the subject whether the subject wishes to notify his/her primary care physician about participation in the study. If the subject agrees to such notification, the Principal Investigator will inform the subject's primary care physician about the subject's participation in the clinical study.

14.4. STUDY DOCUMENTATION

Study documentation includes but is not limited to source documents, case report forms (CRFs), monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder", which includes but is not limited to signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data, which is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the

pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

An electronic case report form (CRF) will be the primary data collection document for the study. The CRFs will be updated within two weeks of acquisition of new source data. Only approved study staff, including the Principle Investigator, Study medical provider/PA, and Clinical Research Specialist are permitted to make entries, changes, or corrections in the CRF. For paper CRFs, errors will be crossed out with a single line, and this line will not obscure the original entry. Changes or corrections will be dated, initialed, and explained (if necessary). The Principal Investigator or authorized key personnel will maintain a record of the changes and corrections. For electronic CRFs, an audit trail will be maintained by the electronic CRF management system (REDCap).

14.5. PRIVACY, CONFIDENTIALITY, AND DATA STORAGE

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate institutional Site Based Research group.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research-related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Subjects will be identified only by a unique study number and subject initials. Electronic records of subject data will be maintained using a dedicated database, REDCap[78], which is approved for research use by Duke IRB. Access to electronic databases will be limited to key personnel. Additionally, the study team will use the Data Access Group feature available in REDCap. This feature allows identified study team members to only see their relevant patients. Specifically, the different sites in this trial will only be able to access the data associated with the participants in their Data Access Group.

Subject data may be stored temporarily on encrypted and password-protected portable memory devices such as flash drives and external hard drives, but only when absolutely necessary. Data stored on portable memory devices will be de-identified. Subject data will be deleted from the portable memory device at the earliest opportunity. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy.

Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

14.6. DATA AND SAFETY MONITORING

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to Sections 11 and 12.

14.7. PROTOCOL AMENDMENTS

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB and submitted to the IND prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB, FDA, and all other applicable regulatory agencies of such action immediately.

14.8. RECORDS RETENTION

The Principal Investigator will maintain study-related records for at least six years after study completion.

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15. APPENDICES

APPENDIX 1: Exclusionary Medication

Information regarding exclusionary medications can be found in Appendix 1, which is a separate document. This document will be provided to the Duke IRB as a separate document. This list will be updated yearly. Any changes made to the medication exclusion list will be at the discretion of the study medical provider.

APPENDIX 2: Demographics/Contact Information Form

Age _____ Date of Birth _____

Gender: ○ Male ○ Female ○ Transgender Female ○Transgender Male ○Other (please specify) ○Prefer not to answer

Marital Status

○ Single, never married
○ Married or domestic partnership
○ Widowed
○ Divorced
○ Separated

Race

○ White
○ Black or African American
○ Asian
○ Native Hawaiian or Other Pacific Islander
○ American Indian or Alaska Native
○ Other (please specify)
○ More than one race

Ethnicity ○ Hispanic or Latino ○ Not Hispanic or Latino

What is the highest level of schooling you have completed?

○ Elementary school or less
○ Some high school
○ High school graduate or equivalent
○ Some college or technical/vocational school
○ College graduate or higher

What is the highest level of schooling you have completed?

○ Employed for wages
○ Self-employed
○ Out of work and looking for work
○ Out of work but not currently looking for work
○ A homemaker
○ A student

○ Military ○ Unable to work

○ Retired

Contact Information Form

First Name _____ M.I. _____ Last Name _____

Number and Street Address _____

City_____ State _____ Zip code _____

Email address _____

Primary Telephone # _____ Other Telephone # _____

Do you give Center for Smoking Cessation permission to leave a message at the above numbers or contact you by email?

○ Yes
○ No

If I cannot be reached or if there is an emergency, you can leave a message with:

Name: _____

Relationship: _____

Telephone #: _____

□ **I understand in the event that I do not return messages and fail to come to appointments my emergency contact person may be contacted.**

APPENDIX 3: Smoking History Questionnaire

Please answer the following questions are about your history of smoking, use of other products and medications.

1. Do you smoke at least 1 cigarette each day?
   1 = Yes
   0 = No

2. (If answered "Yes" do Q1) How many cigarettes do you smoke each day on average? _____ [1-99]
3. (If answered "No" do Q1) How many cigarettes do you smoke each week on average? _____ [1-99]
4. How many years have you smoked? _____ [1-99]

Calculated Field in REDCap: Pack Years: Number of cigarettes per week (Q2)/20 x years smoked (Q4). (Q2 is divided by 20 because there are 20 cigarettes in a pack). Calculated Field in REDCap: Pack Years: Number of cigarettes per week (Q3)/140 x years smoked (Q4).

5. Are you willing to attempt to quit smoking in the next 30 days?

   1 = Yes
   0 = No

6. Do you usually smoke menthol or non-menthol cigarettes?

   1 = Non-Menthol
   2 = Menthol
   3 = Both
   99 = Don't know

7. Does your spouse/partner smoke?

   1 = Yes

   2 = No

   3 = Do not have a spouse/partner

   99 = Don't know

8. If you decided to quit, how likely would the people close to you support your decision to quit?

   1 = Not likely at all

   2 = Very unlikely

3 = Somewhat unlikely

4 = Neither likely nor unlikely

5 = Somewhat likely

6 = Very likely

7 = Extremely likely

99 = Don't know

9. How many times in your life have you stopped smoking for one day or longer because you were trying to quit smoking? _____ [0-99]

10. Have you used the following tobacco products in the last week? (Select all that apply)

1 = Cigarettes

2 = Cigars

3 = Pipes

4 = Hookah

5 = Cigarillos

6 = E-cigarettes

7 = Chewing tobacco

8 = Orbs/sticks/sheets

9 = Snuff

10 = Other

11. During the last week, did you use any of the following drugs? (Select all that apply)

0 = None

1 = Marijuana

2 = Cocaine/Crack

3 = Meth

4 = PCP

5 = Heroin

6 = Other (please specify)

12. During the last week, did you use an opiate such as Codeine, Morphine, MS Contin, OxyContin, Oxycodone, Percocet, Hydrocodone, Vicodin, Hydromophone, Dilaudid, Duragesic or Fentanyl?

1 = Yes
0 = No
99 = Don't know

10. During the last week, did you use a benzodiazepine such as Lorazapam, Ativan, Valium, Alprazolam, Xanax, Clonazepam or Klonopin?

1 = Yes
0 = No
99 = Don't know

APPENDIX 4: Self-efficacy/Motivation

1) On a scale from 1-10, how *confident* are you that you can quit smoking?

1	2	3	4	5	6	7	8	9	10
Not at all		A little		Moderately			Very		Extremely

2) On a scale from 1-10, how *motivated* are you to quit smoking?

1	2	3	4	5	6	7	8	9	10
Not at all		A little		Moderately			Very		Extremely

APPENDIX 5: Patient Health Questionnaire-9[64,65]

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

	Not at all	Several Days	More than half the days	Nearly Everyday
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down.	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television.	0	1	2	3
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	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3

Total: _____ + _____ + _____

Total Score: _____

Scoring (add sum of total scores):

0-4: Minimal Depression

5-9: Mild Depression

10-14: Moderate Depression

15-19: Moderately Severe Depression

20-27: Severe Depression

APPENDIX 6: Columbia Suicide Severity Rating Scale-Screener (C-SSRS)[64]

COLUMBIA-SUICIDE SEVERITY RATING SCALE
Screen Version - Recent

SUICIDE IDEATION DEFINITIONS AND PROMPTS	Past month	
Ask questions that are bolded and underlined.	**YES**	**NO**
Ask Questions 1 and 2		
1) ***Have you wished you were dead or wished you could go to sleep and not wake up?***		
2) ***Have you actually had any thoughts of killing yourself?***		
If YES to 2, ask questions 3, 4, 5, and 6. If NO to 2, go directly to question 6.		
3) ***Have you been thinking about how you might do this?*** E.g. "*I thought about taking an overdose but I never made a specific plan as to when where or how I would actually do it....and I would never go through with it.*"		
4) ***Have you had these thoughts and had some intention of acting on them?*** As opposed to "*I have the thoughts but I definitely will not do anything about them.*"		
5) ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***		

6) ***Have you ever done anything, started to do anything, or prepared to do anything to end your life?***	YES	NO
Examples: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump; or actually took pills, tried to shoot yourself, cut yourself, tried to hang yourself, etc.		
If YES, ask: ***Was this within the past three months?***		

- Low Risk
- Moderate Risk
- High Risk

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APPENDIX 7: Generalized Anxiety Disorder 7-item Scale (GAD-7)[93,94]

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

	Not at all	Several days	Over half the days	Nearly everyday
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total: _____+ _____+ _____

Grand Total: _____

Scoring (add sum of columns)

0-5: Minimal to no anxiety

6-10: Moderate anxiety

11 or above: High anxiety

APPENDIX 8: Alcohol Use Disorders Identification Test (AUDIT)[67]

The Alcohol Use Disorders Identification Test: Self-Report Version

PATIENT: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Place an X in one box that best describes your answer to each question.

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

APPENDIX 9: Medical History

Major Medical Conditions:

○ Yes ○ No High blood pressure (Hypertension)

○ Yes ○ No Heart attack OR heart disease diagnosis by coronary angiogram

○ Yes ○ No Problems with heart valves such as regurgitation, stenosis, or artificial valve

○ Yes ○ No Heart rhythm problem such as atrial fibrillation, tachycardia, or pacemaker

○ Yes ○ No Heart failure requiring a diuretic (water pill)

○ Yes ○ No Skin problems requiring medication

○ Yes ○ No Liver cirrhosis (with jaundice or swollen abdomen)

○ Yes ○ No Liver problems other than cirrhosis (e.g. hepatitis, fatty liver)

○ Yes ○ No Kidney failure requiring dialysis

○ Yes ○ No Chronic Kidney Disease not requiring dialysis

○ Yes ○ No Chronic diarrhea due to 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) (Emphysema)

○ Yes ○ No Asthma

○ Yes ○ No Other chronic lung disorder such as Tuberculosis, Pulmonary Fibrosis, Sarcoid, or other

○ Yes ○ No Stroke/TIA (mini-stroke)

○ Yes ○ No Seizure disorder

○ Yes ○ No Regular headaches

○ Yes ○ No Unexplained fainting spells

○ Yes ○ No Insomnia requiring medications

○ 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, or other

○ Yes ○ No Sinusitis/ Seasonal allergies

○ Yes ○ No Diabetes requiring insulin or other medications

O Yes O No Thyroid disease/condition

O Yes O No Cancer

O Yes O No Depression/Anxiety/Bipolar disorder

O Yes O No Suicidal ideation (thinking about ways to commit suicide) within the past year

O Yes O No Suicide attempt during your lifetime

O Yes O No Schizophrenia

O Yes O No Post-Traumatic Stress Disorder (PTSD)

O Yes O No Other Psychiatric problems (Borderline, Schizoaffective, Hypomania, ADHD)

O Yes O No Chronic infections syndrome such as HIV, CMV, Epstein Barr

MEDICAL HISTORY

Please list any hospitalizations in the past 10 years. If possible, include the year:

1. _____ Year: _____
2. _____ Year: _____
3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

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

1. _____ Year: _____
2. _____ Year: _____
3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

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

1. _____ Year: _____
2. _____ Year: _____

3. _____ Year: _____
4. _____ Year: _____
5. _____ Year: _____

Women Only:

Date of last menstrual cycle: _____ ○ Not Applicable
Are you menstruating regularly? ○ Yes ○ No
Are you post-menopausal (natural or from surgery)? ○ Yes ○ No

Are you willing to use medically acceptable contraceptive measures for the duration of the study?
○ Yes ○ No (○ Not Applicable – PA/MD Initials: _____)

Acceptable methods of contraception include (1) surgical sterilization (such as tubal ligation or hysterectomy, (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as rhythm method or Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

MEDICAL HISTORY

Family History

Has any first degree family member (child, parent, or sibling) had any of the following illnesses?

Illness	Circle One	Which family member?
Anemia or Blood Disease	Yes or No	
Cancer	Yes or No	

Diabetes	Yes or No	
Heart Disease	Yes or No	
High Blood Pressure	Yes or No	
Severe Mental Illness	Yes or No	
Stroke	Yes or No	
Substance Abuse (alcohol, tobacco, or other)	Yes or No	
Other Serious Illness	Yes or No	

Social History

Do you drink alcohol (e.g. beer, wine, liquor)? ○ **Yes** ○ **No**

If YES, how many days per week do you have a drink containing alcohol? _____

How many drinks do you have on your heaviest drinking day of the week? _____

Do you currently drink coffee and / or tea? ○ **Yes** ○ **No**

If YES, how many cups per day? _____

Have you used a non-prescription drug such as marijuana, cocaine or heroin in the last month? ○ **Yes** ○ **No**

If YES, what drug / substance? _____

General Health

1. Do you use oxygen? ○ No ○ Yes, continuously ○ Yes, for exertion or sleep

2. Can you walk up two flights of stairs?

○ No ○ Yes, without stopping ○ Yes, but I would need to stop along the way

3. How well do you walk?

○ I walk independently ○ I walk with a cane ○ I walk with a walker ○ I use a wheelchair

4. Have you ever experienced a seizure or a seizure like activity? ○ Yes ○ No

MEDICAL HISTORY

Name of Medication	Dosage	Start Date	Stop Date	What is the medication used for?
1.				
2.				
3.				
4.				
5.				
6.				
7.				
8.				

Medications

Please list any medications you are allergic to:

1.	2.	3.

Please list all medications you are taking or have used in the last month (includes over-the-counter drugs, vitamins, and prescriptions).

Have you participated in a research study in the past 30 days where you were given medications?

○ **Yes** ○ **No**

Smoking Cessation Medications

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

	Not Used	Used	Side Effects Please list any side effects you experienced while taking any of the medications.	Stopped due to side effects?	
				Yes	No
Nicotine Patch	○	○		○	○
Nicotine Gum	○	○		○	○
Nicotine Lozenge	○	○		○	○
Nicotine Inhaler	○	○		○	○
Zyban (Wellbutrin, Bupropion)	○	○		○	○
Chantix (Varenicline)	○	○		○	○
Have you used any of these medications in the past 7 days? ○ Yes ○ No					

APPENDIX 10: Physical Exam/Review of Systems (ROS)

Review of Systems – Page 1

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

General:
- ○ None of these apply
- ○ Unexplained weight loss or gain
- ○ Fever or chills
- ○ Fatigue / lack of energy
- ○ Weakness
- ○ Trouble sleeping

Skin:
- ○ None of these apply
- ○ Rashes
- ○ Lumps
- ○ Color change
- ○ Hair and nail changes

Head:
- ○ None of these apply
- ○ Headache
- ○ Head injury

Ears:
- ○ None of these apply
- ○ Decreased hearing
- ○ Earache
- ○ Ringing in the 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

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APPENDIX 10: Physical Exam/Review of Systems (ROS) cont…

Review of Systems – Page 2

Urinary:
- ○ None of these apply
- ○ Frequency
- ○ Urgency
- ○ Blood in urine
- ○ Pain with urination
- ○ Change in urinary strength
- ○ Incontinence

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
- ○ 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

PA / MD Signature _____ Date _____

APPENDIX 11: Minnesota Nicotine Withdrawal Scale (MNWS)[65]

Behavior Rating Scale- Self-Report

Please rate yourself for the period for the last 24 hours.

DSM – 5 Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
1. Angry, irritable, frustrated	0	1	2	3	4
2. Anxious, nervous	0	1	2	3	4
3. Depressed mood, sad	0	1	2	3	4
4. Difficulty concentrating	0	1	2	3	4
5. Increased appetite, hungry, weight gain	0	1	2	3	4
6. Insomnia, sleep problems, awakening at night	0	1	2	3	4
7. Restlessness	0	1	2	3	4
Other Validated Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
8. Desire or craving to smoke	0	1	2	3	4
Other Possible Symptoms	**None**	**Slight**	**Mild**	**Moderate**	**Severe**
9. Constipation	0	1	2	3	4
10. Coughing	0	1	2	3	4
11. Decreased pleasure from events	0	1	2	3	4
12. Dizziness	0	1	2	3	4
13. Drowsy	0	1	2	3	4
14. Impatient	0	1	2	3	4
15. Impulsive	0	1	2	3	4

TOTAL Score Questions 1-15: _____

APPENDIX 12: Fagerström Test of Nicotine Dependence[66]

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

    3 = Within 5 minutes

    2 = 6-30 minutes

    1 = 31-60 minutes

    0 = More than 60 min

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

    0 = No

    1 = Yes

3. Which cigarette would hate most to give up?

    1 = The first one in the morning

    0 = All others

4. How many cigarettes per day do you smoke?

    0= 10 or less

    1= 11-20

    2= 21-30

    3= 31 or more

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

    0 = No

    1 = Yes

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

    0 = No

    1 = Yes

Total Score: _____

Scoring (add sum of all scores):

1-2: Low dependence

3-4: Low-moderate dependence

5-7: Moderate dependence

8+: High Dependence

APPENDIX 13: Positive and Negative Affect Schedule (PANAS)[67]

Positive and Negative Affect Schedule (PANAS-SF)

Indicate the extent you have felt this way over the past week.		Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
PANAS 1	Interested	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 2	Distressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 3	Excited	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 4	Upset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 5	Strong	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 6	Guilty	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 7	Scared	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 8	Hostile	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 9	Enthusiastic	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 10	Proud	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 11	Irritable	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 12	Alert	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 13	Ashamed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 14	Inspired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 15	Nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 16	Determined	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 17	Attentive	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 18	Jittery	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 19	Active	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 20	Afraid	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Scoring: Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect. Mean Scores: 33.3 (SD±7.2)

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect. Mean Score: 17.4 (SD ± 6.2)

Your scores on the PANAS: Positive: ____ Negative:

APPENDIX 14: Center for Epidemiologic Studies Depression Scale (CESD)[68]

Below is a list of the ways you might have felt or behaved. How often you have felt this way during the past week?

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family or friends.				
4. I felt I was just as good as other people. 5. I had.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people dislike me.				
20. I could not get "going."				

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

APPENDIX 15: Perceived Stress Scale (PSS-4)[69,70]

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you felt that you were unable to control the important things in your life?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

2. In the last month, how often have you felt confident about your ability to handle your personal problems?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

3. In the last month, how often have you felt that things were going your way?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

APPENDIX 16: Recent Smoking Questionnaire

The follow questions are about your recent smoking

1. In the last 30 days, have you smoked at all - even a puff?

    1 = Yes

    0 = No

    99 = Don't know

2. In the last 7 days, have you smoked at all - even a puff?

    1 = Yes

    0 = No

    99 = Don't know

3. In the last 7 days, how many days did you smoke cigarettes? _____ [0-7]

4. In the last 7 days, how many cigarettes have you smoked per **day?** _____ [0-99]

APPENDIX 17: Mood and Physical Symptoms Scale-2 (MPSS-2)[71]

The next questions are about how you have been feeling over the past 24 hours.

1. How much of the time have you felt the urge to smoke in the past 24 hours?

   0=Not at all

   1=A little of the time

   2=Some of the time

   3=A lot of the time

   4=Almost all of the time

   5= All of the time

2. How strong have the urges been?

   0=No urge

   1=Slight

   2=Moderate

   3=Strong

   4=Very Strong

   5=Extremely Strong

Total: _____

Scoring (sum of questions):

0-2: Mild

3-6: Moderate

7-10: Severe

APPENDIX 18: Modified Cigarette Evaluation Questionnaire (mCEQ)[72]

If you have smoked since you last completed this questionnaire, please mark the number that best represents how smoking made you feel.

(1—not at all, 2—very little, 3—a little, 4—moderately, 5—a lot, 6—quite a lot, 7—extremely).

1. Was smoking satisfying? _____

2. Did cigarettes taste good? _____

3. Did you enjoy the sensations in your throat and chest? _____

4. Did smoking calm you down? _____

5. Did smoking make you feel more awake? _____

6. Did smoking make you feel less irritable? _____

7. Did smoking help you concentrate? _____

8. Did smoking reduce your hunger for food? _____

9. Did smoking make you dizzy? _____

10. Did smoking make you nauseous? _____

11. Did smoking immediately relieve your craving for a cigarette? _____

12. Did you enjoy smoking? _____

Scoring Subscales:

1. "Smoking Satisfaction" (items 1, 2, 12)
2. "Psychological Reward" (items 4-8)
3. "Aversion" (items 9, 10)
4. "Enjoyment of Respiratory Tract Sensations" (item 3)
5. "Craving Reduction" (item 11).

Scores for each subscale are calculated as the average of its individual item responses.

Higher scores indicate greater intensity of each smoking effect with, for example, greater satisfaction or psychological reward after smoking.

APPENDIX 19: QUESTIONNAIRE OF SMOKING URGES (QSU-BRIEF)[73,74]

Please rank each item on a scale from 1-7

1 = Strongly Disagree

2

3

4 = Agree

5

6

7 = Strongly Agree

1. I have a desire for a cigarette right now.
2. Nothing would be better than smoking a cigarette right now.
3. If it were possible, I probably would smoke now.
4. I could control things better right now if I could smoke.
5. All I want right now is a cigarette.
6. I have an urge for a cigarette.
7. A cigarette would taste good now.
8. I would do almost anything for a cigarette right now.
9. Smoking would make me less depressed.
10. I am going to smoking as soon as possible.

Factor 1 (Intention/Desire to Smoke) included items 1, 3, 6, 7, and 10

Factor 2 (Relief of Negative Affect and Urgent Desire to Smoke) included items 2, 4, 5, 8, and 9

Factor 3 (Combined) included 1, 6 (from Factor 1) and 4, 8, 9 (from Factor 2).

Sum answers and higher score indicates stronger smoking urges.

APPENDIX 20: SMOKING AND MEDICATION USE[75,76]

Duke Center for Smoking Cessation
Study Name: Project Q Pilot Varenicline
Principal Investigator: James M. Davis M.D.

Subject Number: QPV_____
Subject Initials: _____

Visit 1 – Visit 2: Medication Diary

Medication Instructions: Take one Chantix/Placebo pill in the morning with breakfast.
Take one Chantix/Placebo pill in the evening with dinner.

If you experience any side effects, or have questions, call **Jordan at (919) 668-1327** or our main line at (919) 668-5055.

Day	Date	# of Cigarettes Smoked	Medication Use Bottle #: _____
1 Visit 1 Date	____/____	_____	
2	____/____	_____	START MEDICATION ○ Morning Dose ○ Evening Dose
3	____/____	_____	○ Morning Dose ○ Evening Dose
4	____/____	_____	○ Morning Dose ○ Evening Dose
5	____/____	_____	○ Morning Dose ○ Evening Dose
6	____/____	_____	○ Morning Dose ○ Evening Dose
7	____/____	_____	○ Morning Dose ○ Evening Dose

Day	Date	# of Cigarettes Smoked	Medication Use Bottle #: _____
8	____/____	_____	○ Morning Dose ○ Evening Dose
9	____/____	_____	○ Morning Dose ○ Evening Dose
10	____/____	_____	○ Morning Dose ○ Evening Dose
11	____/____	_____	○ Morning Dose ○ Evening Dose
12	____/____	_____	○ Morning Dose ○ Evening Dose
13	____/____	_____	○ Morning Dose ○ Evening Dose
14	____/____	_____	○ Morning Dose ○ Evening Dose
Visit 2 Date			

*Will be modified for the ramp up period as necessary.

APPENDIX 21: MEDICATION SIDE EFFECTS QUESTIONNAIRE

Duke Center for Smoking Cessation; Study Name:

Principal Investigator: James M. Davis M.D.

Subject Number: _____

Subject Initials: _____

Date of Visit: _____

Medication Side Effects Questionnaire

Have you experienced any side effects from the study drugs you are taking? ○ **Yes** ○**No**

If yes, and fill out the information below.

Side Effect 1:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 2:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? (mm/dd/yy)				**How long did it last (number of days)?**			
Side Effect 3:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely

	When did it start? **(mm/dd/yy)**				**How long did it last (number of days)?**			
Side Effect 4:	**Frequency**	Just once	A Few Times	Several Times	Every Day	More than Once a Day		
	Severity	1 Not at All	2 Very Little	3 A Little	4 Moderately	5 A Lot	6 Quite a lot	7 Extremely
	When did it start? **(mm/dd/yy)**				**How long did it last (number of days)?**			

IF YOU REPORTED SIDE EFFECTS ABOVE:

Did you stop the study medication as a result of the side effect(s) you listed above? O YES O NO

APPENDIX 22: TEXT BASED MESSAGING

Introduction

Description	Question	Answer options
Introduction	Thank you for being in the Project Q - a program to help light smokers quit.	NA
Date Reminder1	Starting on DATE, please text us the letter S every time you smoke.	
Date Reminder 2	Starting on DATE, please text us the letter C every time you have a craving.	

Texted "S"

Description	Question	Answer options
Confirm Smoking1	You just smoked? Text back Y or N.	YES or NO
Craving1	How much did you crave the cigarette you just smoked? On a scale from 1-10.	Range: 1 = Not at all, 10 = Very, very much
Stress1	How stressed did you feel just before you smoked? On a scale from 1-10.	Range: 1 = Not at all, 10 = Very, very stressed
Mood1	What is your mood? On a scale from 1-10.	Range: 1 = Extremely bad, 10 = Extremely good
Satisfaction1	How satisfying was the cigarette you just smoked? On a scale from 1-10.	Range: 1 = Not at all, 10 = Very satisfying
People1	Are you by yourself? Text back Y or N.	YES or NO
People1.1	If not alone, how many people are you with? Enter number between 1-100.	Range 1-100.
Place 1	Where are you: 1= home; 2 = work, 3 = public place; 4 = driving/walking; 5 = other	1-5

Food1	Did you eat or drink anything in the past 15 minutes? Text back Y or N.	YES or NO
Alcohol1	Did you consume alcohol in the past 2 hours? Text back Y or N.	YES or NO
Thank you1	Thanks for answering those questions.	NA

Texted "C"

Description	**Question**	**Answer options**
Craving2	How strong is your craving? On a scale from 1-10.	Range: 1 = Not at all, 10 = Very, very strong
Stress2	How stressed are you? On a scale from 1-10.	Range: 1 = Not at all, 10 = Very, very stressed
Mood2	What is your mood? On a scale from 1-10.	Range: 1 = Extremely bad, 10 = Extremely good
People2	Are you by yourself? Text back Y or N.	YES or NO
People2.1	If not alone, how many people are you with? Enter number between 1-100.	Range 1-100.
Place 2	Where are you: 1= home; 2 = work, 3 = public place; 4 = driving/walking; 5 = other	1-5
Food2	Did you eat or drink anything in the past 15 minutes? Text back Y or N.	YES or NO
Alcohol2	Did you consume alcohol in the past 2 hours? Text back Y or N.	YES or NO
Smoke2	Did you smoke a cigarette in response to this episode of craving? Text back Y or N.	YES or NO
Thank you2	Thanks for answering those questions.	NA

Overall (End of Day)

Description	**Question**	**Answer options**

Overall	How many cigarettes did you smoke today?	#0-100
Adherence AM	Did you take the morning dose of your study medication today?	YES or NO
Adherence PM	Did you take the evening dose of your study medication today?	YES or NO

APPENDIX 23: PHONE CALL FOLLOW-UP QUESTIONS

1. Have you smoked at all in the last 7 days YES or NO
2. In the past 7 days, have you smoked at least 1 cigarette? YES or NO
    a. (If YES) In the past 7 days, how many cigarettes have you smoke each day on average? _____
    b. (If NO) How many cigarettes have you smoked in total in the past 7 days? _____
3. Have you taken your medication as directed? YES or NO
4. Are you having side effects associated with the medication you received in this study? YES or NO
5. If so - what side effects? (notes box)