wcg IRB

Certificate of Action

Investigator Name: Scott James Leischow, PhD	**Board Action Date:** 03/03/2021
Investigator Address: Arizona State University, 425 N 3rd Street Phoenix, AZ 85004, United States	**Approval Expires:** 02/21/2022 **Continuing Review Frequency:** Annually
Sponsor: National Institutes of Health (NIH) **Institution Tracking Number:**	**Sponsor Protocol Number:** 1R01DA044125 **Amended Sponsor Protocol Number:**
Study Number: 1183046	**IRB Tracking Number:** 20180219
Work Order Number: 1-1404472-1	
Protocol Title: Varenicline OTC Trial on Efficacy and Safety	

THE FOLLOWING ITEMS ARE APPROVED:
Phone Screen Form - In Person #17243352.2 - As Submitted
Phone Screen Form - Remote #30052000.0 - As Submitted
Revised Protocol (01-26-2021)
Consent Form - ASU - In Person [IN8]
Consent Form - ASU - Remote Cohort [IN0]
Advertisement - Print (ASU) In Person- Are you a smoker who #17243355.3 - As Submitted
Advertisement - Print (ASU) Remote - Are you a smoker who #30052004.0 - As Submitted
Advertisement - Print (LACT) In Person- Are you a smoker who #17243356.3 - As Submitted
Advertisement - Print (LACT) Remote - Are you a smoker who #30052016.0 - As Submitted
Advertisement - Social Media (LACT) In Person- Are you a smoker who #26596570.1 - As Submitted
Advertisement - Social Media (LACT) Remote - Are you a smoker who #30052012.0 - As Submitted
Advertisement - Social Media In Person - Any one of the following #26596569.1 - As Submitted
Advertisement - Social Media Remote - Any one of the following #30052005.0 - As Submitted
Revised Research Locations (02-18-2021) x1
Telephone Screening Script - LACT In Person #17243354.3 - As Submitted
Telephone Screening Script- In Person #17243353.3 - As Submitted
Telephone Screening Script Remote - LACT #30052008.0 - As Submitted
Telephone Screening Script Remote #30052006.0 - As Submitted

Please note the following information:
NOTE: IRB currently has CHANTIX (varenicline) Tablets Prescribing Information (12-2016) on file.

Please have all future subjects sign the Consent Form(s) specified in this approval.

THE IRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:
Arizona State University, School of Nutrition and Health Promotion, Healthy Lifestyles Research Center, 425 N. 5th Street, Phoenix, Arizona 85004
Los Angeles Clinical Trials, 847 North Hollywood Way, Suite 103, Burbank, California 91505
Arizona State University, 850 N 5th Street, Phoenix, Arizona 85004

ALL IRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:
As a requirement of IRB approval, the investigators conducting this research will:

- Comply with all requirements and determinations of the IRB.

This is to certify that the information contained herein is true and correct as reflected in the records of WCG IRB. WE CERTIFY THAT WCG IRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) REGULATIONS, AND THE INTERNATIONAL CONFERENCE ON HARMONISATION (ICH) GUIDELINES.

Association for the Accreditation of Human Research Protection Programs, Inc. Full Accreditation

- Protect the rights, safety, and welfare of subjects involved in the research.
- Personally conduct or supervise the research.
- Conduct the research in accordance with the relevant current protocol approved by the IRB.
- Ensure that there are adequate resources to carry out the research safely.
- Ensure that research staff are qualified to perform procedures and duties assigned to them during the research.
- Submit proposed modifications to the IRB prior to their implementation.
    - Not make modifications to the research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.
- For research subject to continuing review, submit continuing review reports when requested by the IRB.
- Submit a closure form to close research (end the IRB's oversight) when:
    - The protocol is permanently closed to enrollment
    - All subjects have completed all protocol related interventions and interactions
    - For research subject to federal oversight other than FDA:
        - No additional identifiable private information about the subjects is being obtained
        - Analysis of private identifiable information is completed
- For research subject to continuing review, if research approval expires, stop all research activities and immediately contact the IRB.
- Promptly (within 5 days) report to the IRB the information items listed in the IRB's "Prompt Reporting Requirements" available on the IRB's Web site.
- Not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
- Not accept payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments") without prior IRB approval.
- When required by the IRB ensure that consent, permission, and assent are obtained and documented in accordance with the relevant current protocol as approved by the IRB.
- Promptly notify the IRB of any change to information provided on your initial submission form.

Consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization shall promptly communicate or provide, the following information relevant to the protection of human subjects to the IRB in a timely manner:

- Upon request of the IRB, a copy of the written plan between sponsor or CRO and site that addresses whether expenses for medical care incurred by human subject research subjects who experience research related injury will be reimbursed, and if so, who is responsible in order to determine consistency with the language in the consent document.
- Any site monitoring report that directly and materially affects subject safety or their willingness to continue participation. Such reports will be provided to the IRB within 5 days.
- Reports from any data monitoring committee, data and safety monitoring board, or data and safety monitoring committee in accordance with the time frame specified in the research protocol.
- Any findings from a closed research when those findings materially affect the safety and medical care of past subjects. Findings will be reported for 2 years after the closure of the research.

For Investigator's Brochures, an approval action indicates that the IRB has the document on file for the research.
If the IRB approved an e-consent process that involves uploading the approved consent form to an e-consent platform, please ensure that the consent form(s) approved for your site is the version of the consent form that gets uploaded to the platform.
If the board approves a change of Principal Investigator - Once approved, the new Principal Investigator is authorized by WCG IRB to carry out the study as previously approved for the prior Principal Investigator (unless the Board provides alternate instructions to the new Principal Investigator). This includes continued use of the previously approved study materials. The IRB considers the approval of the new PI a continuation of the original approval, so the identifying information about the study remains the same.

If your research site is a HIPAA covered entity, the HIPAA Privacy Rule requires you to obtain written authorization from each research subject for any use or disclosure of protected health information for research. If your IRB-approved consent form does not include such HIPAA authorization language, the HIPAA Privacy Rule requires you to have each research subject sign a separate authorization agreement. "

For research subject to continuing review, you will receive Continuing Review Report forms from WCG IRB when the expiration date is approaching.

Thank you for using this WCG IRB to provide oversight for your research project.

DISTRIBUTION OF COPIES:
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Ginger Hook, Arizona State University

COA Template 12-2020

Ramya Turaga, PhD, Arizona State University

Date: **January 26, 2021**

Protocol Title: Varenicline OTC Trial on Efficacy and Safety

Protocol ID #: 1R01DA044125
Granting Agency: National Institute of Health/National Institute on Drug Abuse
Agency Address: 6001 Executive Blvd # 5128,
Rockville, MD 20852

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A. BACKGROUND & SIGNIFICANCE

Overview - Tobacco Cessation Treatments

Tobacco use kills 480,000 individuals in the United States each year.[1] Morbidity and mortality from tobacco use dwarfs all other preventable causes of mortality (alcohol, accidents, homicide, etc.) combined[2] Most tobacco users want to quit, yet unlike other individuals who are dependent on illicit drugs or alcohol, they rarely seek formal treatment from physicians or cessation programs.[3] Instead, most tobacco users attempt to go "cold turkey" and most fail numerous times before quitting.[4,5] In fact, on any quit attempt, only about 6% of smokers achieve long-term success.[6]

At present, there are five forms of NRT available in the U.S. (gum, patch, lozenge, nasal spray and inhaler), and two forms of non-nicotine medication (bupropion and varenicline [brand name Chantix™]). Quit rates can be doubled using cessation medications,[7,8] yet despite the known efficacy of NRT and direct to consumer marketing by pharmaceutical companies, fewer than one in five smokers use some form of NRT during a quit attempt, either prescribed by a health care provider or over-the-counter (OTC).[9] Although some studies indicate that OTC medications significantly increase success at quitting when compared to using no medication,[10] multiple studies have questioned whether OTC NRT is effective for smoking cessation.[11-13]

Multiple studies, including meta-analyses and the recent large trial directly comparing varenicline, bupropion and nicotine patch, show that varenicline is the single most effective medication for smoking cessation.[14-24] However, because it requires a prescription and fear of the box warning required by the FDA (see below), use of varenicline has been lower than NRT even though it is significantly more effective. Now that the box warning has been removed (Chantix™ label update, December 2016), it is essential to move more smokers who want to quit onto varenicline so that we can decrease smoking prevalence at an increased rapid pace.

Varenicline History

Varenicline acts as a partial agonist and does not produce the same intensity of response as a full agonist, even at high doses. Thus, the drug is classified as a selective nicotine receptor partial agonist (SNRPA) that works both to stimulate the nicotine receptor and block smoking reward at the α4β2 nicotinic receptor subtype.[22] Of the many nicotine receptor subtypes, the α4β2 receptor is thought to mediate the rewarding properties of nicotine by modulating the release of dopamine in the nucleus accumbens (NA), or so-called "pleasure center" of the brain. In addition to its agonist effect, varenicline also has a powerful competitive antagonist effect on nicotine, due primarily to a substantially higher affinity for the α4ß2 receptor.[22]

Efficacy of Varenicline. Studies have demonstrated the efficacy of varenicline, both in comparison with placebo[14-24] and in comparison with the other FDA-approved smoking cessation medications.[17] The USPHS and Cochrane meta-analyses found that varenicline results in the highest quit rates of any cessation medication mono therapy. Additionally the recent EAGLES study[17] that compared varenicline, bupropion and nicotine patch in over 8000 smokers with and without a history of psychiatric conditions showed clearly that in a head-to-head study, varenicline is the single most effective medication.

The dose of varenicline approved by the FDA for smoking cessation is 1mg b.i.d. What many scientists and clinicians seem to have missed is that a Phase II study completed by Oncken et al[18] prior to the FDA approval showed that .5mg b.i.d. - half the dose of varenicline now recommended – appears to be as effective as the FDA-approved 1mg b.i.d. dose and results in fewer side effects. In the Oncken et al[6] study, participants received behavioral intervention at each visit, so it was not an OTC study, but given these results, it is

important to assess the optimal dose to achieve efficacy while at the same time minimize side effects.

Safety of Varenicline. Early studies on varenicline suggested that it was safe to use, with nausea, insomnia, abnormal dreams, headaches and flatulence and vomiting the most commonly reported side effects in the phase 2 and 3 studies.[24] However, anecdotal post-marketing reports of psychiatric adverse events including suicidal ideation and suicidal behavior led the FDA to require a box warning for varenicline in 2008.[25-28] At the same time, the FDA required a similar box warning for bupropion, another prescription smoking cessation medication. The label change led to significantly less use of varenicline. Multiple studies (observational and RCTs) completed over the past eight years have provided strong evidence that the prevalence of these adverse events (AEs) was no greater than for placebo or NRT.[28-30] Pfizer requested that the FDA drop the box warning based on these results. However, the FDA had earlier required the implementation of the largest smoking cessation clinical trial ever conducted – which compared the safety and efficacy of varenicline, bupropion and nicotine patch to placebo – and indicated that they would not consider removing the box warning until the results of that study were available. The results of that study, called EAGLES, were recently published.[17] They clearly show that 1 mg b.i.d. varenicline is as safe as nicotine patch and bupropion for smoking cessation, and that it is more effective than both. In addition, in a currently unpublished study, we have analyzed the outcomes of over 116,000 smokers prescribed varenicline via the large Optum Labs clinical dataset, and those analyses reinforce the Eagles study: IDC9 coding showed that fewer than 1% of those with and without a pre-existing psychiatric diagnoses experienced suicidal ideation or suicide attempts after they were prescribed varenicline. Given these new results, both the FDA and the European Union have removed the box warning from varenicline, but the Warning and Precaution for potential psychiatric side effects still remains.

Other rare safety concerns in the package insert include seizures, new or worsening heart or blood pressure problems, sleepwalking, increased sensitivity to alcohol, and serious allergic or skin reactions.

Our Research on Rx to OTC switch. Our team has conducted multiple clinical trials to assess the safety and efficacy of smoking cessation medications as potential OTC products. With funding from NIDA, Leischow et al randomized smokers to receive nicotine patch in either an OTC condition or a health care provider (HCP) intervention.[12] Finally, in the only study published to date on the efficacy of switching the nicotine inhaler from Rx to OTC,[11] we randomized smokers (n=500) to either an OTC or Rx condition and found that the Rx group had significantly higher quit rates at each time point than the OTC group except at week 52, and the OTC group quit rates were only 6% at one year (similar to using no medication).

Dr. Nides enrolled 550 subjects in a 3-site nicotine patch OTC switch study in 1994. The study compared 6 weeks of 21mg patches versus placebo in a quasi-OTC storefront or office-building environment. At the end of treatment,16.8% in the active group vs. 9.6% in the placebo group had quit smoking. In a comparison arm in which participants paid to receive active patches, the quit rate was 19%.

Lastly, both Dr. Nides and Leischow recently recruited over 170 participants at each of their sites on a large multi-center clinical trial assessing the safety and efficacy of a nicotine mouth spray, the result of which are not yet available.

What each of these studies have in common is exploring whether a smoking cessation can be effective and safe when provided without behavioral support. The focus of the current study is to likewise assess whether varenicline can be safe and effective when no behavioral support is provided.

B. SPECIFIC AIMS

Three of the NRT products (i.e. patch, gum, and lozenge) are available as over-the-counter (OTC) products because clinical trials have shown that they are safe and effective without healthcare provider involvement. The other two NRT products are not OTC for different reasons. The nasal spray has not been formally tested, perhaps because it is aversive when first used and has some potential for abuse liability. The nicotine inhaler is not effective as an OTC medication.[1]

The two non-nicotine prescription medications, varenicline and bupropion, have not been considered for OTC status, in part because both had a 'box warning' placed on them by the FDA due to concerns that their use might cause or exacerbate psychiatric symptoms such as suicidal ideation or behavior. After multiple studies, including one of the largest smoking cessation trials ('EAGLES' study) ever conducted,[17] it is clear that these medications do not cause statistically higher psychiatric adverse events than placebo or NRT. More specifically, in the EAGLES study, the FDA-approved dose of varenicline was found significantly more effective than bupropion, patch and placebo, and did not result in adverse events that necessitates a box warning, so the FDA removed the box warning. Thus, in combination with behavioral support, varenicline has the greatest probability of helping the most smokers quit with a similar adverse event profile to current OTC NRT products.

Given these data, the time has come to explore whether varenicline is safe and effective when no behavioral support is provided as a foundation to assessing whether it can be safe and effective as an over-the-counter medication. This is important because in real world use, smokers often do not receive behavioral support, so there is value in assessing whether varenicline quit rates will still be high without that behavioral support. Moreover, since the adverse events from varenicline have been shown to be comparable to the OTC nicotine patch, this research will assess whether varenicline, in two different doses, can be safe and effective without a healthcare provider prescription. More specifically, because earlier research found that .5mg twice a day (b.i.d.) varenicline is as effective as the currently FDA-approved 1.0mg b.i.d. dosing but with lower incidence of nausea and sleep disturbance[6], there is value in assessing whether the lower dose will work as well as the higher dose in an OTC environment. Lastly, to understand the within-person mechanisms explaining *how* and *when* OTC varenicline might improve cessation outcomes, as well as how side effects affect medication adherence, we will also assess experience with OTC varenicline via ecological momentary assessment (EMA).

Primary Objectives

1. To assess the safety and efficacy of the current FDA-approved 1 mg b.i.d. varenicline for smoking cessation in comparison with placebo when used in a simulated OTC study with no behavioral support provided.
2. To assess the safety and efficacy of .5mg b.i.d. varenicline in comparison with 1mg b.i.d. varenicline and placebo when used in a simulated OTC study with no behavioral support provided.

Secondary Objectives

1. To evaluate whether subject specific characteristics (e.g. socioeconomic status, ethnicity, smoking history, etc.) moderate primary (safety and efficacy) and secondary (adherence) outcomes.
2. To evaluate medication use patterns to assess whether varenicline is being used as indicated on the label, and to determine if medication adherence mediates cessation outcomes between-subjects.

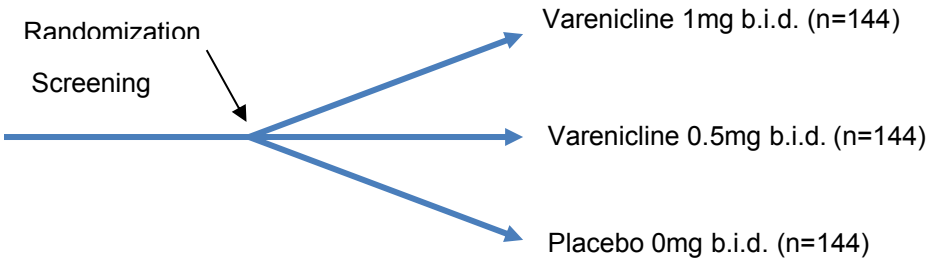
3. In a subsample of participants, to examine how medication adherence, withdrawal, and side effects (e.g. nausea and sleep disturbance) vary within-subjects and are associated with smoking status using EMA in the first two critical weeks of medication use.

Hypotheses
1. Quit rates in the 1 mg b.i.d. varenicline condition will be significantly higher than the placebo medication condition when provided as an OTC medication.
2. Quit rates in the .5 mg b.i.d. varenicline condition will be comparable to the 1mg b.i.d. varenicline condition, and will be significantly higher than the placebo medication condition, when provided as an OTC medication.
3. Side effects will show a dose response relationship, with effects lowest in the placebo group.

C. EXPERIMENTAL METHODS

Study Design

The primary objective of this study is to assess the efficacy of two different doses of varenicline used in a simulated OTC intervention relative to placebo (total N = 432). The design is a three-group placebo-controlled, double blind, block randomized clinical trial (as indicated in the figure), where participants will be randomly assigned to one of three conditions: (1) 1 mg b.i.d. varenicline for 12 weeks, which is the current FDA-approved dose, (2) 0.5 mg b.i.d. varenicline for 12 weeks, or (3) placebo.



In addition, we will collect EMA data from 25 participants in each condition to obtain more granular data on the momentary relationship between varenicline use, adverse events, smoking, craving, and mood in the critical first two weeks after medication use begins. Outcomes of greatest interest are the within-person relationships between medication use (e.g., adherence), medication safety (e.g., adverse events), quit rates (self-report and biochemically validated), and factors that are associated with specific treatment outcomes.

Study sites

This study will be implemented at both Los Angeles Clinical Trials (LACT) and the Arizona State University. Dr. Nides will implement the study in Los Angeles; Dr. Leischow will implement the study in Phoenix.

Human Subjects Protection. Western IRB (WIRB) will be the IRB of record for this study, and the ASU IRB will receive the WIRB approvals and maintain documentation because it is the institution that has received funding from NIH. WIRB approval is required for study implementation. WIRB will maintain records for the study, and the ASU IRB will maintain a copy.

Recruitment. We are making changes below due to the COVID-19 pandemic. The COVID-19 pandemic has resulted in a drop in the number of potential participants contacting both sites in response to recruitment advertisements. Due to the lower number of respondents, we would like to increase the geographical area from which we are recruiting. By allowing for

remote participation, we will we recruit nationally in addition to local site recruitment for in-person participation.

There will be two cohorts for this study going forward: one in-person cohort, and one remote cohort. We will recruit both cohorts via paid and free (e.g. Craigslist, Facebook, etc.) advertisements, as we have for other studies. We anticipate, based on previous studies, that we will need to recruit well over 2500 potential participants, of which 700 will be screened before 432 will ultimately be randomized. Fortunately, both sites can draw from large local populations that are demographically diverse.

Participants. We will recruit male and female smokers of any race/ethnicity who are at least 21 years of age (with no upper age limit). Our anticipated recruitment plan is: 60% male, 80% white, 10% black, 7% American Indian/Alaska Native, and 3% Hispanic. No vulnerable populations (eg incarcerated, mentally handicapped, etc) will be included; the specific inclusion/exclusion are below.

Procedures by Study Visit for the In-person Cohort
The Study Flow Chart and Schedule of Activities (Table 1) summarizes the data collection that will occur at each visit. The procedures that will occur at each visit are the following:

Table 1. Study Flow Chart and Schedule of Activities for in-person visits

Protocol Activity	Screening/ Baseline	Follow- up Visits (Week #s)					End of Study Visit
		2	4	8	12	13	26
Informed consent	X						
Inclusion/Exclusion criteria	X						
Randomization	X						
Assignment of ID number	X						
Demographics	X						
Medical history	X						
Body weight and height	X				X		X
Vital signs, e.g. blood pressure	X						
REALM test of health literacy	X						
Smoking and cessation medication history	X						
FTCD	X						
Urine pregnancy test	X						
Urine drug screen	X						
Breath CO	X		X	X	X		X
Smoking status/Resource Utiliz.		X	X	X	X	X	X
Minnesota Craving and Withdrawal symptoms (MNWS)	X	X	X	X	X	X	X
mCEQ		X	X	X	X		
Provide Product Information	X						
Investigational product dispensed	X		X	X			
Investigational product retrieved			X	X	X		

Adherence and Efficacy Assessment		X	X	X	X		
Adverse events		X	X	X	X	X	X
Previous and Concomitant Medications	X	X	X	X	X	X	X
Suicidal Behavior Questionnaire	X						

Initial telephone contact for the In-person Cohort: Potential participants will be asked to call a local or toll-free phone number to enroll. During this phone call, potential participants will be screened to assess eligibility based on the inclusion/exclusion criterion. Those still interested and qualified will be scheduled for the screening/baseline study visit and given directions to the study site. In addition to the eligibility screen, potential participants will also be screened for symptoms of COVID-19 (see COVID-19 Safety Procedures document) and have new safety procedures explained to them.

Screening/Baseline for the In-person Cohort
When potential participants arrive at the research site, the study will be described in written format and orally by study staff, and participants will be asked to sign the consent form. Participants will be asked to follow the guidelines outlined in the COVID-19 Safety Procedures document. The following will occur during Screening/Baseline:

- Informed Consent
- Subject Demographics (see Appendix 1)
- Smoking, tobacco, and cessation medication use history (see Appendix 2)
- Rapid Estimate of Adult Literacy in Medicine (REALM, see Appendix 3)
- Minnesota Nicotine Withdrawal Scale (MNWS, see Appendix 4). This brief staff or subject administered form will assess cigarette-related craving and withdrawal.
- Medical History—Pertinent medical history will be assessed and documented on the Medical History CRF by the study coordinator through a review of systems, allergies, and recent surgeries
- Previous and Concomitant Medications. Medications taken within the previous 30 days of the Screening/Baseline visit will be documented in the Concomitant Medication CRF
- Body weight and height-height in meters (to the nearest cm) and weight in kilograms (to the nearest 0.1 kg in light indoor clothing and without shoes will be measured.
- Vital signs including blood pressure and heart rate, measured after the subject has been seated and resting for at least 5 minutes.
- Fagerström Test of Cigarette Dependence (FTCD, see Appendix 7). This 5 item subject completed questionnaire measures dependence on cigarettes.
- Urine pregnancy test for all females
- Urine drug screen. The urine test for drugs of abuse (eg opiates, amphetamines, benzodiazepines, cocaine or other substances) will be performed only at the Screening/Baseline Visit. Subjects who test positive will be excluded, unless they can provide the clinic with a copy of a current prescription for opioids or stimulants.
- A portion of this urine will be stored for exploratory analysis of nicotine and nicotine metabolism that might be related to treatment outcomes, only at the ASU site.
- Breath Carbon Monoxide test. The breath CO will be collected after a 15 second breath hold using the Bedfont Micro Plus (Bedfont Inc).

- If the subject requires study approval from their own physician, the Investigational Product will be dispensed upon their return to the clinic with the signed authorization (Appendix 8)
- If subject meets all inclusion and exclusion criterion, a study ID will be assigned and he/she will be randomized in a 1:1:1 fashion to 1.0 mg b.i.d. varenicline, .5mg b.i.d. varenicline, or placebo. Participants and study staff will be blinded to the assignment.
- Investigational Product educational information will be provided to participants
- The first five weeks of Investigational Product dispensed
- If randomized into the substudy, subjects will be instructed on how to respond to the text messages
- Suicidal Behavior Questionnaire (Appendix 15)

Week 2 Visit for the In-person Cohort

- Telephone call
- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status and Resource Utilization Assessment (See Appendix 9) (Brief site administered questionnaires assessing smoking status, smoking cessation resources used since last study visit
- Medication Adherence, and Perceived Efficacy Assessment (see Appendix 10) (Brief site administered questionnaires assessing pills taken since last study visit, and perceived efficacy of the medication.
- Modified Cigarette Evaluation Questionnaire (mCEQ), see Appendix 11). This 15-item staff or subject administered questionnaire assesses the degree to which smokers experience the reinforcing effects of smoking.

Weeks 4, 8 for the In-person Cohort

- Breath Carbon Monoxide test
- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status, and Resource Utilization Assessment
- Medication adherence and Perceived Efficacy Assessment
- Assess medication use by retrieving unused medication
- Modified Cigarette Evaluation Questionnaire (mCEQ)
- Dispense additional Investigational Product

**All questionnaires at this visit will take place, as much as possible, on the phone prior to the subject attending the visit as to minimize contact in response to the COVID-19 pandemic*

Week 12 for the In-person Cohort

- Body weight
- Breath Carbon Monoxide test
- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status, and Resource Utilization Assessment

- Medication Adherence and Perceived Efficacy Assessment
- Assess medication use by retrieving unused medication
- Modified Cigarette Evaluation Questionnaire (mCEQ)

**All questionnaires at this visit will take place, as much as possible on the phone prior to the subject attending the visit as to minimize contact in response to the COVID-19 pandemic*

Week 13 (telephone call) for the In-person Cohort

- Smoking Status, and Resource Utilization Assessment
- Adverse Events
- Minnesota Nicotine Withdrawal Scale
- Concomitant Medications including Chantix™ or other smoking cessation aids

Week 26 for the In-person Cohort

- Telephone call
- Smoking Status and Resource Utilization Assessment
- Body weight
- Breath Carbon Monoxide test

Visit Window. Table 2 shows the target and allowed windows for study visits. Except for Week 2 where the telephone visit should be no more than 2 days on either side of the target visit day, the allowed window for each visit is 5 days before or after the target visit. Visits outside of those ranges are allowed, but must be documented (eg vacation, difficulty contacting, illness, etc).

Table 2. Target and allowed windows for study visits for the In-person and remote cohorts.

Visit Week	Target Day in Relation to Randomization Date	Allowed Window (days)
BL		
2 (call)	14	12-16
4	28	23-33
8	52	47-57
12	98	93-103
13 (call)	105	100-110
26	182	177-187

Inclusion Criteria for the In-person Cohort

1. 21 years of age or older
2. Self-reported daily smoker
3. Breath CO > 10ppm
4. Motivated to quit smoking completely within five weeks of the Screening Visit (>5 on reported motivation)
5. Capable of and agree to complete study requirements
6. Literate in English, self-report

7. Must be available for the duration of study
8. Informed consent obtained
9. Willing and able to provide additional data between visits using ecological momentary assessment (EMA)
10. Must own study compatible smart-phone (iPhone or Android)

Exclusion Criteria for the In-person Cohort

1. Any self-report, diagnosis or treatment of heart attack, unstable angina, angioedema, seizures, cerebrovascular accident (CVA) within the last six months.
2. Any self-report, diagnosis or treatment of bipolar, schizophrenia or suicidal ideation within the last six months. (For suicidal ideation a score of ≥7 on the Suicidal Behavior Questionnaire, see Appendix 15)
3. Self-report of diagnosis or treatment for depression within the past six months, unless participant has written permission by their healthcare provider to participate
4. Systolic blood pressure 160 or higher and/or diastolic blood pressure 100 or higher (see site applicable SOP for Evaluating and Reporting Blood Pressure and Appendices 5 and 6 for participant handouts)
5. History of renal disease
6. Allergy to any of the ingredients in varenicline
7. Participation in another smoking cessation program or any type of clinical trial in the past 3 months
8. Use of any smoking cessation medication in the past three months
9. Any other medical condition(s) which the licensed study physician deems unacceptable for participation in this study
10. Positive drug screen indicating possible substance abuse (eg opiates, amphetamines, benzodiazepines, cocaine or other substances), unless participant can show that the medication has been prescribed by licensed clinical provider.
11. Consume greater than 21 alcohol drinks per week.
12. No two members of the same household may participate in this study
13. No study staff or their immediate family may participate in the study
14. Females who are pregnant, breast feeding, or not currently using a medically approved form of birth control and unwilling to do so.
Acceptable methods of birth control include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring, and condoms.

Procedures by Study Visit for the Remote Cohort

The Study Flow Chart and Schedule of Activities (Table 3) summarizes the data collection that will occur at each visit. The procedures that will occur at each visit are the following:

Table 3. Study Flow Chart and Schedule of Activities **for the Remote Cohort**

Protocol Activity	Screening/ Baseline 1	Screening/ Baseline 2	Follow- up Visits (Week #s)					End of Study Visit
			2	4	8	12	13	26
Informed consent	X							
Inclusion/Exclusion criteria	X							

Randomization		X						
Assignment of ID number		X						
Demographics	X							
Medical history	X							
REALM test of health literacy	X							
Smoking and cessation medication history	X							
FTCD	X							
Urine pregnancy test		X						
Urine Cotinine		X			X*	X*		X*
Smoking status/Resource Utiliz.			X	X	X	X	X	X
Minnesota Craving and Withdrawal symptoms (MNWS)	X		X	X	X	X	X	X
mCEQ			X	X	X	X		
Provide Product Information		X						
Investigational product dispensed		X						
Investigational product retrieved						X		
Adherence and Efficacy Assessment			X	X	X	X		
Adverse events			X	X	X	X	X	X
Previous and Concomitant Medications	X		X	X	X	X	X	X
Suicidal Behavior Questionnaire	X							

* Only if they report not smoking

Initial telephone contact for the Remote Cohort: Potential participants will call a local or toll-free phone number to enroll. During this phone call, potential participants will be screened to assess eligibility based on the inclusion/exclusion criterion. Those still interested and qualified will be scheduled for the screening/baseline study visit.

Screening/Baseline for the Remote Cohort – Visit 1
A time will be scheduled for a phone call or Zoom meeting, the study will be described in written format and orally by study staff, and participants will be asked to electronically sign the consent form. The following will occur during Screening/Baseline:

- Informed Consent (electronic)
- Subject Demographics (see Appendix 1)
- Smoking, tobacco, and cessation medication use history (see Appendix 2)
- Rapid Estimate of Adult Literacy in Medicine (REALM, see Appendix 3)
- Minnesota Nicotine Withdrawal Scale (MNWS, see Appendix 4). This brief staff or subject administered form will assess cigarette-related craving and withdrawal.
- Medical History—Pertinent medical history will be assessed and documented on the Medical History CRF by the study coordinator through a review of systems, allergies, and recent surgeries
- Previous and Concomitant Medications. Medications taken within the previous 30 days of the Screening/Baseline visit will be documented in the Concomitant Medication CRF
- Fagerström Test of Cigarette Dependence (FTCD, see Appendix 7). This 5 item subject completed questionnaire measures dependence on cigarettes.

- If the subject requires study approval from their own physician, the Investigational Product will be dispensed upon receipt of the signed authorization (Appendix 8)
- Suicidal Behavior Questionnaire (Appendix 15)

Screening/Baseline for the Remote Cohort – Visit 2

- Urine pregnancy test for all females. This will be mailed to the participant after they have completed Screening/Baseline Visit 1.
- Urine cotinine test. This will be mailed to the participant after they have completed Screening/Baseline Visit 1.
- If subject meets all inclusion and exclusion criterion, a study ID will be assigned and he/she will be randomized in a 1:1:1 fashion to 1.0 mg b.i.d. varenicline, .5mg b.i.d. varenicline, or placebo. Participants and study staff will be blinded to the assignment.
- Investigational Product educational information will be provided to participants
- The Investigational Product will be dispensed to be used for the full 12 weeks of treatment
- Participants will have 30 days from the start of their first screening visit to complete all the procedures and begin the medication
- Participants will be asked to contact study staff when they receive the study medication to inform staff when they will be starting the medication so they remaining visits can be based on the medication start date.

Week 2 Visit for the Remote Cohort

- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status and Resource Utilization Assessment (See Appendix 9) (Brief site administered questionnaires assessing smoking status, smoking cessation resources used since last study visit
- Medication Adherence, and Perceived Efficacy Assessment (see Appendix 10) (Brief site administered questionnaires assessing pills taken since last study visit, and perceived efficacy of the medication.
- Modified Cigarette Evaluation Questionnaire (mCEQ), see Appendix 11). This 15-item staff or subject administered questionnaire assesses the degree to which smokers experience the reinforcing effects of smoking.

Week 4 Visit for Remote Cohort

- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status, and Resource Utilization Assessment
- Medication adherence and Perceived Efficacy Assessment
- Modified Cigarette Evaluation Questionnaire (mCEQ)

Week 8 Visit for the Remote Cohort

- Urine cotinine test, if they report not smoking
- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications

- Smoking Status, and Resource Utilization Assessment
- Medication adherence and Perceived Efficacy Assessment
- Modified Cigarette Evaluation Questionnaire (mCEQ)

Week 12 for the Remote Cohort
- Urine cotinine test, if they report not smoking
- Minnesota Nicotine Withdrawal Scale
- Adverse Events
- Concomitant Medications
- Smoking Status, and Resource Utilization Assessment
- Medication Adherence and Perceived Efficacy Assessment

- Assess medication use by asking the participants to mail back any unused study medication
- Modified Cigarette Evaluation Questionnaire (mCEQ)

Week 13 for the Remote Cohort
- Smoking Status, and Resource Utilization Assessment
- Adverse Events
- Minnesota Nicotine Withdrawal Scale
- Concomitant Medications including Chantix™ or other smoking cessation aids

Week 26 for the Remote Cohort
- Telephone call
- Smoking Status and Resource Utilization Assessment
- Urine cotinine test, if they report not smoking

Visit Window for the Remote Cohort. Will be the same as shown in Table 2.

Inclusion Criteria for the Remote Cohort

1. 21 years of age or older
2. Self-reported daily smoker
3. Positive cotinine from urine sample
4. Motivated to quit smoking completely within five weeks of the Screening Visit (>5 on reported motivation)
5. Capable of and agree to complete study requirements
6. Literate in English, self-report
7. Must be available for the duration of study
8. Informed consent obtained
10. Must own study compatible smart-phone (iPhone or Android)
11. Must be a current resident of the United States

Exclusion Criteria for the Remote Cohort

1. Any self-report, diagnosis or treatment of heart attack, unstable angina, angioedema, seizures, cerebrovascular accident (CVA) within the last six months.

2. Any self-report, diagnosis or treatment of bipolar, schizophrenia or suicidal ideation within the last six months. (For suicidal ideation a score of ≥7 on the Suicidal Behavior Questionnaire, see Appendix 15)
3. Self-report of diagnosis or treatment for depression within the past six months, unless participant has written permission by their healthcare provider to participate
4. History of renal disease
5. Allergy to any of the ingredients in varenicline
6. Participation in another smoking cessation program or any type of clinical trial in the past 3 months
7. Use of any smoking cessation medication in the past three months
8. Any other medical condition(s) which the licensed study physician deems unacceptable for participation in this study
9. Consume greater than 21 alcohol drinks per week.
10. No two members of the same household may participate in this study
11. No study staff or their immediate family may participate in the study
12. Females who are pregnant, breast feeding, or not currently using a medically approved form of birth control and unwilling to do so.
    Acceptable methods of birth control include abstinence, oral contraceptives, the contraceptive patch, the contraceptive ring, and condoms.

Behavioral Support

No behavioral support will be provided by the study team at any visit. At all follow-up visits post-randomization, they will not be given encouragement by study staff to quit smoking, nor be provided with any information or instruction about medication usage other than consent form and Chantix Use and Safety Information handout (see Appendix 12). We will assess at each visit whether subjects used any behavioral support available in the community.

Risk/Benefit Assessment

Risk Category. Greater than minimal risk

Potential Risk. The most recent data found that varenicline does not result in greater risk than nicotine patch, which is already an over-the-counter medication, and that led the FDA to remove the box warning on varenicline. The most common side effects of varenicline are: nausea, sleep problems (trouble sleeping, vivid, unusual, or strange dreams), constipation, and gas and/or vomiting, and there is a very small risk that a participant could develop an allergic reaction to varenicline. In addition, the product warnings indicate that: “Some people have had new or worse mental health problems, such as changes in behavior or thinking, aggression, hostility, agitation, depressed mood, or suicidal thoughts or actions while taking or after stopping varenicline. These symptoms happened more often in people who had a history of mental health problems. Some people have had seizures during treatment with varenicline. New or worse heart or blood vessel problems can happen with varenicline. Sleepwalking can happen with varenicline, and can sometimes lead to harmful behavior.[31]”

Participants might also experience withdrawal symptoms from quitting smoking, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain.

Protection Against Risks. Product information provided to participants will encourage them to use the product with a full glass of water after eating a meal. The product information will encourage use caution when using machinery or driving, and to

decrease alcohol consumption. In addition, information on symptoms associated with an allergic reaction will be provided. In addition, we will monitor participants at every visit to assess any potential adverse events, they will have a phone number that can be called at any time to contact study investigators, and they will be followed after they have discontinued medication to assess any effects for up to three months after medication completion.

Potential Benefits to the Subjects. The potential benefits to participants are substantial because it could help them to quit smoking, which is the leading preventable cause of death in the US.

Alternatives to Participation. Any of those who are not eligible for the study will be referred to the free smoking cessation quitline available in both states. In addition, any participants who elect to drop out of the study will also be referred to the state quitline, or could potentially obtain Chantix or another medication from their healthcare provider.

Investigational Product

Product: Varenicline (generic name, product name is Chantix™)
Doses: 0.0 mg, .5mg and 1.0 mg
Product Form: Pill
Product Administration: Oral, with water
Manufacturer: Pfizer

Varenicline and Placebo. In this study, participants will be randomly assigned in double-blind fashion to use one of two doses of varenicline (.5 mg b.i.d. or 1.0mg b.i.d.) or placebo (see study design above). Both varenicline and the placebo will look identical and be in identical packaging.

Medication Dosing. Participants assigned to the 1.0 mg b.i.d. condition, which is the current FDA-recommended dosing, will follow the recommended varenicline titrated dosing schedule as follows: days 1 through 3: 0.5mg, one daily; days 4 through 7: 0.5mg, twice daily; days 8 through end of treatment: 1mg, twice daily. Those assigned to the 0.5mg bid. condition will begin use 0.5mg once daily days 1 through 3, then will begin using 0.5 b.i.d on day 4 through the end of the study. Those assigned to the placebo condition will use pills that look identical to those that are being used in the other conditions but contain no medication. The subjects in the placebo group will also titrate during the first 7 days (1 pill days 1-3, 2 pills for the duration of the treatment period). All participants will take identical looking pills at the same time throughout the study, with the only difference being the amount of varenicline included in each pill.

Product Packaging. Medication packaging for this study will be implemented at the ASU site. Two study staff will work together to package the medications, and all packaging will be double checked and tracking forms maintained by the staff to assure quality control. Medications will be shipped by FedEx or equivalent to LACT (or directly to participants if they are participating in the study remotely), where study product will be checked and a report provided back to ASU within 24 hours indicating whether all sent medications were received.

Product will be packaged for each in-person cohort study visit as follows: (1) Baseline to Week 4: During the first week after baseline, when participants start and ramp up their dose, standard multi-compartment pill organizer containers will be provided to study participants with their assigned dosing regimen (as indicated above). In addition, participants will be provided 28 days of their maintenance twice daily dose in a standard child resistant-pill bottle. This will allow for an extra 7 days of IP to account for delays in attending the Week 4 visit. (2) Week 4 and Week 8: Medication will be provided in a pill

bottle at each visit, and in order to assure adequate supply in case of a delay in study visits, each container will contain enough product to last 5 weeks. All containers will be child-resistant for added protection, and labeled appropriately for the study.

Product will be packaged **for the remote cohort** as follows: product will be mailed after the second baseline visit. The first week of starting the medication, when participants start and ramp up their dose, standard 7-day multi-compartment pill organizer containers will be provided to study participants with their assigned dosing regimen (as indicated above). In addition, participants will be provided 12 weeks of their maintenance twice daily dose in a standard child resistant-pill bottle. All containers will be child-resistant for added protection, and labeled appropriately for the study.

Product Education Information. When participants are provided Investigational Product the first time (Screening/Baseline 1 or 2), they will be given a consumer-friendly handout, Chantix Use and Safety Information (Appendix 12) that includes information on how to use the medication, smoking cessation withdrawal symptoms, side effects and adverse events, and information on smoking cessation quitlines. This handout is a modification of the FDA-approved Chantix Medication Guide (Appendix 14), which was modified to meet needs of the study. The handout will include information on setting a quit date that exists on the Chantix™ website. The recommendation will be to set a quit date for Day 8 of medication use, or up to 30 days after starting the study product. Note that participants in all study conditions will have product available for a maximum of 12 weeks. If participants wish to use the medication beyond 12 weeks, they will need to contact their own health care provider for a prescription that they can fill at their own expense. We will assess at each follow-up visit whether any participants used varenicline beyond the 12 weeks of this study.

Blinding. Our statistician will create the code that will allow identification of which numbered product is varenicline or placebo, and the code will be maintained in a sealed envelope in a locked cabinet by the ASU and LACT study sites that can be readily accessed in case of emergencies.

Medication Cost. There will be no medication cost to participants. Because some of the participants will receive placebo, charging for the product would not be reasonable. In addition, this design is consistent with the approach approved by the FDA when testing NRT OTC studies, so we want to use a design that has potential relevance to the FDA.

Adverse Events

Handling Adverse Events. Multiple very large studies have demonstrated that varenicline has a safety profile that is very similar to NRT[5]. Clinical trials to date indicate that varenicline utilization results in very few serious adverse events. However, we will take tracking and management of adverse events very seriously (as we have in our previous studies). As indicated above, we will make sure to assess adverse events that might reflect exacerbation of any reported or unreported psychiatric disorders.

Adverse Event (AE) Definitions. Any negative event subsequent to signing consent but prior to the week 13 visit will be considered a potential adverse event to be addressed and followed, regardless of whether it is related to use of study medication. Examples of AEs include: (1) Clinical signs and symptoms, (2) Abnormal test results, (3) Worsening of existing medical conditions. The licensed medical professional (LMP) will consider adverse events serious if the event: (1) is life threatening, (2) results in death, (3) leads to incapacity, hospitalization, or serious impairment of normal life, (4) congenital abnormality or birth defect. Serious AEs will be reported to the IRB within 24 hours of the site becoming aware of the event. Once an adverse or serious adverse event is identified, it must be followed and recorded, such that subsequent to the designation each event

outcome should be characterized as follows: 1 = Still present, 2 = Resolved with Sequelae, 3 = Resolved without Sequelae, 4 = Lost to follow-up/Unknown, 5 = Death.

Determination of Severity. The study coordinators will make a determination of AE severity and provide a grade for each event according to the following criterion: Mild: Symptoms cause little discomfort, are easily tolerated, and do not significantly interfere with normal everyday activities. Moderate: Symptoms are uncomfortable and interfere with normal everyday activities. Severe: Symptoms cause significant impairment of everyday activities, incapacitation, or death

Determination of Causality. The LMP will make a determination the causality of each adverse event in relation to the study medication using the following criteria: 1 = Definite, 2 = Probable, 3 = Possible, 4 = Remote, 5 = Definitely Not

Process for Handling AEs. At each visit and post-cessation call (and via EMA, see sub-study below), every participant will be asked to report on health status and adverse events. In addition, study participants will be instructed verbally and in writing to contact the study staff immediately if any health problem causes disruption in the participant's life – though participants will be informed to call 911 if they are experiencing any potentially life-threatening problems. Calls to the study staff will be triaged to determine if the study LMP should be contacted. The Arizona State University and LACT study physicians will address any medical problems that might arise (including working with each participant's health care provider if needed).

AE Reporting Period. All events not resolved or unrecovered by week 13 will be followed for 30 days after that date to assess status. Any participants lost to follow-up after a reported AE or serious AE will have 'unknown' indicated for that event.

Participant Payment

Main Study and Sub-studies. Note that all study participants will receive compensation for time and/or travel to the study sites as well as completing telephone visits during the treatment and follow-up study phases. Participants in the in-person cohort will be paid $50 compensation for the screening/baseline visit, $25 compensation for completing each of the weeks 2 and 13 telephone visits, $50 for completing the in-clinic visits at weeks 4 and 8, and $100 for completing the in-clinic week 12 visit (total of $250), regardless of their smoking status. In addition, study participants will be compensated $50 to come into the study sites to complete electronic questionnaires and to provide a breath CO if they report 7-day point prevalence abstinence at the 6-month follow-up call. Given the attrition that occurs in many smoking cessation studies, especially those that assess OTC medications, compensation for key study visits is essential.

Participants in the Remote Cohort will be paid $50 combined for screening/baseline visits 1 and 2, $25 compensation for completing each of the weeks 2 and 13 visits, $50 for the visits at weeks 4 and 8, and $100 for completing the week 12 visit (total for $200), regardless of their smoking status. In addition, remote study participants will be compensated $50 electronic questionnaires and to provide a urine sample for cotinine analysis if they report 7-day point prevalence abstinence at the 6-month follow-up call. Compensation will be paid to participants electronically.

Participants in the sub-studies will also be compensated. (1) EMA sub-study: Participants (total N = 75, or 25/medication condition) in the EMA sub-study will receive an additional $30 for completion of Week 1 EMA assessments and $40 for Week 2 EMA assessments. To encourage compliance with the EMA protocol and decrease incidence of missing data, sub-study participants will receive an additional $10 in Weeks 1 and 2 if they complete 6 of 7 daily diaries, and will receive an additional $10 in Weeks 1 and 2 if they respond to at least 3 scheduled prompts a day in each week. In total, EMA participants will

be compensated an additional $70 to $110 at the Week 4 visit, depending on protocol compliance.

EMA Sub-Study

Methods. We will randomly assign 25 people from each condition to participate in the EMA sub-study that lasts two weeks after the participants begin using varenicline, and they will be informed in the consent form at the Baseline/Screening visit that they may be asked to participate in the sub-study. We will use two types of EMA data assessments: (1) evening daily diaries to collect information on concrete behaviors (e.g., smoking and taking medication) that occurred that day, and (2) scheduled prompts to assess states (e.g. mood, craving, nausea) that fluctuate throughout the day (Appendix 13). Data will be collected using scheduled text messages linked to Qualtrics, which provides HIPPA-compliant data collection. At the Baseline/Screening visit, the research assistant will enroll substudy participants in the text message EMA data collection and will train participants how to respond to the scheduled prompts and the daily diary EMA surveys. The evening daily diary will include two brief questions on cigarette and varenicline pill consumption that day. In addition to the daily diary, participants will also respond to up to five scheduled prompts throughout the day. The first scheduled prompt will occur at 9am, and will include five brief questions on vivid dreaming and sleep quality from the last night, momentary nausea, momentary mood, and momentary craving. After the first scheduled prompt of the day is completed, subsequent scheduled prompts will ask about momentary nausea, mood, and craving only. Participants will be prompted to complete scheduled surveys at waking and at every four hours. Scheduled prompts will expire 30 minutes after their scheduled time; evening daily diaries can be completed any time after their scheduled time until midnight.

EMA Data Collection Summary. Table 3 shows the information and frequency that will be collected via EMA.

Table 3. EMA schedule of assessments.

	Baseline	**Week**	
		1	2
Assignment to EMA sub study	X		
Subject review of Varenicline Label	X		
Text message instructions	X		
Scheduled prompts			
Vivid dreaming (last night)		X	X
Sleep quality (last night)		X	X
Nausea (current)		X	X
Mood (current)		X	X
Cigarette craving (current)		X	X
Daily diaries			
Number of cigarettes smoked that day		X	X
Varenicline taken that day		X	X
Additional thoughts/feelings?		X	X

EMA compliance and feasibility. The EMA scheduled prompts and daily diary are extremely brief. Similar assessments from Dr. Pearson's Moment Study took typical

participants no more than 90 seconds to complete. To reduce missing data, participants who miss more than two sequential days of evening daily diaries or complete fewer than three scheduled prompts a day for two sequential days will receive encouragement texts and calls from an RA to troubleshoot any problems with the app and encourage compliance.

Definitions of Success

FDA Abstinence Criteria. As indicated earlier, in all studies that assess medications for smoking cessation, the FDA typically requires verification of 28 days of continuous abstinence, i.e.; not a single puff from a single cigarette. The FDA does not require the 'clock' to start at a consistent time point after study enrollment. Thus, in many studies the 'clock' on that 28 days begins two weeks after study medication has begun, while in other studies the 'clock' starts at a different time point. In the current study, we will follow the protocol used in the varenicline pivotal trials.[6,17-20] The primary study outcome in the proposed study will be continuous abstinence between weeks 8 and 12 after study medication has begun. Subjects who are randomized but who never obtain medication will be considered treatment failures and will be included in the denominator in the intent-to-treat analyses.

D. DATA SAFETY MONITORING PLAN

Participant Safety. This study includes the use of a medication, varenicline, that is FDA-approved, as well as the same medication at a lower dose than approved by the FDA, in order to assess whether smokers can choose and use the medication without a healthcare provider prescription. Given the existing data, the likelihood of participants experiencing a serious adverse event from the use of varenicline is very low. In fact, in one of the largest smoking cessation studies ever conducted, the adverse events related to varenicline were similar to those from the nicotine patch, which is already approved as an OTC medication.

However, we will monitor very carefully the screening and ongoing participation of all participants. ~~Study participants will only be allowed to participate and receive medication if the study licensed healthcare provider at each site has approved their participation after reviewing screening documents.~~ Regular visits as well as assessments between visits will provide updates on potential adverse events, and any serious events will be assessed (including for causality) by the study physicians and reported to Western IRB and the study sponsor (National Institute on Drug Abuse/NIH) within 24 hours.

We will also identify an independent safety-monitoring panel (comprised of an MD and two additional scientists to be determined) who receive reports once a year on participant safety, protocol violations, medication use, and any other relevant topics in order to assure patient safety and study integrity. The safety-monitoring panel will assess all adverse events, and will make an independent recommendation on how study staff should address any concerns that they have raised. Their report will be maintained in the study file notebook.

E. DATA MANAGEMENT AND ANALYSIS

Data Collection, Management and Storage. All participant data will be collected and stored on the password protected iPad, and all iPads will be maintained in accordance with Good Clinical Practices and FDA regulations, e.g. in locked cabinets in locked rooms with acess restricted only to study personnel. Once each month, data will be securely sent from LA Clinical Trials to the Arizona State University, where the data will be stored for analysis. We are currently implementing a different study together, and the data transfer has worked well.

Sample Size. The primary analysis of this study is to compare the quit rates between groups. The sample size estimation is based on the results from Oncken et al.[6] the quit rates at 12 weeks for 0.5, 1.0 mg b.i.d. titrated groups and control group are approximately 45%, 60% and 15%. In an OTC setting, we assume the rates would reduce by half. Therefore, 23%, 30% and 8% are used to determine the sample size. Since we are interested in comparing the two active treatment arms with the control arm, to control for the overall type I error rate, the Bonferroni adjustment is applied: for each comparison, the type I error is 0.025. With 110 participants per group, we have at least 80% power to detect a difference of 23% vs. 8% (0.5mg vs. control) by the chi-square test. Even though a smaller sample size is required to detect a difference of 30% vs. 8% (1.0mg b.i.d. vs. control), we plan to enroll equal number of participants for each arm.

For the EMA component of the study, we anticipate the primary outcomes for each treatment condition in the EMA subgroup will not be statistically different from the non-EMA sample and plan to analyze the primary outcomes based on the combined sample. However, the data collected will provide information to quantify the longitudinal within subject association. In particular, we hypothesize that the severity of side effect will increase in the first 5 days after the initiation of treatment, and expect the odds of side effect at day 5 is three times the odds at day 1. Based on our simulations (type I error 0.05, 5 time points, and intra-class correlation 0.3), with 25 participants per group, we have at least 80% power to detect an odds ratio of 3.

Data Sharing Plan. The information that we will collect includes medically-related information that is protected and must remain confidential, so all standard methods to protect participant confidentiality will be employed, including maintaining information in password protected encrypted databases to reduce the risk of a data breach. Shared data across the two study sites will likewise be password protected and encrypted. After study completion, any outside requests for data will require a data sharing agreement that assures the following: (1) all data must be maintained in a secure fashion using appropriate technology, (2) commitment to use the data only for the research purposes requested, and (3) all shared data must either be destroyed or returned, including written assurances to that effect.

Statistical Analysis Plan

Main study. The participation flow will be reported following CONSORT guidelines. Intention to treat analysis will be applied for all statistical analyses. The data collected from the study will be summarized by the descriptive statistics for overall and by treatment condiction (1mg b.i.d., .5mg b.i.d. and placebo) and by the application of EMA (yes/no). The primary analysis will include estimating and comparing the quit rates between treatment arms. We will fit a logistic regression to model the probability of smoking cessation at 12 weeks with treatment condition, application of EMA and the interaction term of the two main effects as independent variables. If the interaction term is not significant, this implies the quit rates for the same treatment condition are similar in those with and without the utilization of EMA, and we will drop the interaction term and fit a model with main effects only. The comparison will be perfromed by the Wald test from the logistic regression with Bonferroni adjustment to account for multiple comparisons. The point estimate of quit rate and 95% confidence interval (CI) for each treatment condition will be reported. If the interaction term is significant, we will conduct the comparisons in EMA and non-EMA subgroups. A similar approach will be applied to the analysis of adherence and adverse events. These two outcome variables can be analyzed as a dichotomous (yes/no) or count variable (pill count and number of adverse events), and the logistic regression and Poisson regression will be used to evaluate whether group differences occur. In the secondary analysis, to evaluate

the impact of participant characteristics on the study outcomes, we will fit multivariable logistic or Poisson regression models. The odds ratio (from logistic regression) and ratio or percent change (from Poisson regression) will be reported to quantify the association.

In addition to evaluting the primary and secondary outcomes at the end of treatment (12 week), the trend over time between the initiation of treatment and at the end of the follow up period is also of interest. We will implement generalized linear mixed model (GLMM) with random intercept to account for the clustering effect (multiple visits clustered within each participant).[32,33] Independent variables will include treatment condition, visit number, and other time-varying characteristics collected post radomization. We intend to use two-level GLMMs, and will perform exploratory analysis using 3-level GLMMs (visits clustered within participants, and participants clustered within sites [CA, AZ]), as we anticipate the variability from sites would be negligible.

Analysis of the Remote Cohort. We will assess the in-person and remote cohort data via separate analyses, but because the fundamental study design in the same for both, if the outcomes of the separate analyses suggest similar outcomes, we might combine the results of both groups into a single analysis.

EMA Statistical Analysis Plan. Our approach to analyzing EMA data is based on published approaches[32,33] using GLMMs. This class of models is useful for analyzing EMA data because they allow multiple observations per subject, multiple levels of nesting (i.e., observations within weeks within subjects), multiple subject random effects, modeling of between-subjects (BS) and within-subjects (WS) variance as a function of time-invariant covariates (e.g. treatment assignment, gender, or nicotine dependence), and extension to non-normal outcomes (i.e., dichotomous, ordinal, counts). Our primary approach will be a three-level mixed model treating observations (level 1) within days (level 2) within subjects (level 3). Additionally, we will employ a time-varying effect model (TVEM)[34] if we find evidence that the relative association between momentary medication adherence, side effects, craving, and smoking varies over the two weeks of observation.[35] We present brief examples of analyses of central interest below.

Our proposed EMA design allows for examination of multiple within-person, longitudinal associations between medication use, side effects, smoking, and craving, thus identifying the mechanisms driving smoking cessation when varenicline is used OTC. (1) The role of time on side effects: H1: Average ratings of day-level side effect severity (e.g. nausea, sleep disturbance, vivid dreams) will increase in the first week of varenicline use. H2: Average within-person change in side effects will be greatest for those in the 1mg b.i.d condition. (2) The role of side effects on medication adherence: H3: Average ratings of day-level side effect severity will predict the odds of day-level medication adherence. (3) The role of medication adherence on momentary craving and smoking: H4: Day-level medication adherence will predict the day-level odds of smoking, mediated by average craving within-person. H5: Day-level medication adherence will predict day-level craving similarly for those in the 1 mg b.i.d and 0.5 b.i.d. conditions, but not the placebo condition.

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G. Appendix

Appendix 1

Demographic Information

1. Gender _____
2. DOB: _____
3. Race (Check all that apply):

   White or Caucasian _____
   Black or African American _____
   Asian_____
   Native Hawaiian or other Pacific Islander _____
   American Indian or Alaska Native_____
   Other_____ (specify)

4. Ethnicity:

   Hispanic_____
   Non-Hispanic_____

5. Highest Level of Education

   Some high school or less_____
   High school graduate or GED_____
   Some college, no degree_____
   Associate's degree_____
   Bachelor's degree_____
   Graduate degree_____

Appendix 2

Nicotine Use History Questionnaire

1. Average number of cigarettes smoked per day during the past 3 months? _____
   a. What brand do you smoke?_____
   b. What size (mm) _____ (70, 72,84, 100,120, other: specify, not applicable)
   c. Menthol or tobacco flavor?_____
      i. Full flavor_____ Medium____ Light____ Ultralight_____
      ii. Package color_____
      iii. Filter____ Non filter____
      iv. Commercially rolled_____ roll your own_____
2. Age started smoking? _____
3. Maximum CPD smoked on average during any one year since started smoking? _____
4. Number of serious quit attempts? _____
5. If >0:
   a. Longest time quit smoking? Years____ Months_____ Days_____
   b. Methods used to quit smoking:
      i. Counseling Yes____ No____
      ii. Nicotine gum Yes____ No____
      iii. Nicotine lozenge Yes____ No____
      iv. Nicotine patch Yes____ No____
      v. Nicotine Inhaler Yes____ No____
      vi. Nicotine nasal spray Yes____ No____
      vii. Chantix Yes____ No____
      viii. Zyban Yes____ No____
      ix. Electronic Cigarette Yes____ No____
6. How many other smokers in your household?_____
7. Other tobacco products used
   a. Ecigarettes/vape Yes____ No____
   b. Hookah Yes____ No____
   c. Cigars Yes____ No____
   d. Smokeless tobacco Yes____ No____
   e. Other (please specify:_____)

Appendix 3

REALM Questionnaire

RAPID ESTIMATE OF ADULT LITERACY IN MEDICINE (REALM)©

List 1			List 2			List 3		
	Correct	**Not Correct**		**Correct**	**Not Correct**		**Correct**	**Not Correct**
Fat			fatigue			allergic		
Flu			pelvic			menstrual		
Pill			jaundice			testicle		
Dose			infection			colitis		
Eye			exercise			emergency		
Stress			behavior			medication		
Smear			prescription			occupation		
Nerves			notify			sexually		
Germs			gallbladder			alcoholism		
Meals			calories			irritation		
disease			depression			constipation		
cancer			miscarriage			gonorrhea		
caffeine			pregnancy			inflammatory		
Attack			arthritis			diabetes		
Kidney			nutrition			hepatitis		
hormones			menopause			antibiotics		
Herpes			appendix			diagnosis		
seizure			abnormal			potassium		
Bowel			syphilis			anemia		
asthma			hemorrhoids			obesity		
Rectal			nausea			osteoporosis		
Incest			directed			impetigo		

Total Score: _____of 66 correct.

Appendix 4

Minnesota Nicotine Withdrawal Scale (MNWS)

MNWS

Please answer the questions based on how you have felt or what you have noticed *in the past week.* Answer based on how you have felt *in general* during this time. Please indicate with an X in the applicable box.

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

Appendix 5

Arizona State University
School of Nutrition and Health Promotion
Healthy Lifestyles Research Center

DATE **Study Name:** Varenicline OTC Trial on Efficacy and Safety

This letter is to communicate the results of a recent measurement of your blood pressure.

Your blood pressure today was _____(systolic) /_____ (diastolic)

The results obtained are outside of the normal range. We recommend you share and discuss these results with your primary care physician or qualified healthcare provider within 5 days or within 24 hours if your blood pressure is above 180 systolic or 120 diastolic.

Below are local options for you to consider for access to care if you do not currently have a primary care provider:

Emergency Rooms:

St. Joseph's Hospital & Medical Center
350 West Thomas Rd
Phoenix, AZ 85013
(602) 406-3000
https://dignity.inquicker.com/next-24/az/phoenix

Banner - University Medical Center Phoenix
1111 E. McDowell Rd
Phoenix, AZ 85006
(602) 839-2000
https://www.clockwisemd.com/hospitals/3253/appointments/new

Urgent Care:

Banner Urgent Care
Camelback & 7th St
5018 N 7th St
Phoenix, AZ 85014
(602) 255-7680
https://urgentcare.bannerhealth.com/

Banner Urgent Care
Indian School & 32nd St
3141 E Indian School Rd #102
Phoenix, AZ 85016
(602) 255-7700

The results do not serve as definitive indicator of health or disease, and as the results of any test need to be evaluated in the context of other factors by a physician or clinician. Therefore, these results do not serve as a diagnosis of any kind for any medical condition and need to be interpreted by a physician or qualified health care provider. By signing below, you agree to share this information with your primary care physician to learn about how these results are relevant to your health and/or disease risk and discuss next steps.

Research Results Acknowledgement Statement

Read and initial each statement below and sign to request your research results:

☐ I understand that test results obtained during research studies are not used for diagnostic purposes.

☐ I understand that it is my responsibility to discuss any results and follow up with my primary care physician or qualified health professional and that neither the study investigator nor research staff will provide interpretation, counseling, consultation, or care recommendations on the basis of any of the research results provided to me. I release from liability and will not hold Arizona State University or the study physician responsible if I do not promptly communicate the results of these tests to my physician.

My signature below confirms the above statements and receipt of my results from participation in the research study entitled:

_____ Signature	_____ Date
_____ Printed Name	
_____ Researcher collecting signature	_____ Date
_____ Printed Name	_____ Phone Number

MY BLOOD PRESSURE MEASUREMENT TODAY:

DATE: _____ BP:_____

The 5 blood pressure ranges recognized by the American Heart Association are:

Blood Pressure Category	Systolic mm Hg (upper number)		Diastolic mm Hg (lower number)
NORMAL	LESS THAN 12O	and	LESS THAN 80
ELEVATED	120-129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130-139	or	80-89
HIGH BLOOD PRESSURE (HYPETERNSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HIGH BLOOD PRESSURE (HYPERTENSION) CRISIS	HIGHER THAN 180	and/or	HIGHER THAN 120

We provide this as a resource.

It is important to manage your blood pressure at a healthy level.

If your blood pressure is higher than 180/120 mm Hg and you are experiencing signs of possible organ damage such as chest pain, shortness of breath, back pain, numbness/weakness, change in vision, difficulty speaking, do not wait to see if your pressure comes down on its own.

Call 9-1-1

For more information about blood pressure contact the American Heart Association:

WWW.Heart.org

Appendix 6

Los Angeles Clinical Trials
847 North Hollywood Way, Suite 103
Burbank, CA 91505 818-526-7645
DATE:_____

Study Name: Varenicline OTC Trial on Efficacy and Safety

This letter is to communicate the results of a recent measurement of your blood pressure.

Your blood pressure today was _____(systolic) /_____ (diastolic)

The results obtained are outside of the normal range. ***We recommend you share and discuss these results with your primary care physician or qualified healthcare provider within 5 days or within 24 hours if your blood pressure is above 180 systolic or 120 diastolic.***

Providence St. Joseph's Medical Center is an option for you to consider for access to care if you do not currently have a primary care provider: It is approximately 2 miles from our clinic.

Providence Saint Joseph Medical Center
501 S. Buena Vista Street
Burbank, CA 91505
818-843-5111

The results do not serve as definitive indicator of health or disease, and as the results of any test need to be evaluated in the context of other factors by a physician or clinician. Therefore, these results do not serve as a diagnosis of any kind for any medical condition and need to be interpreted by a physician or qualified health care provider. By signing below, you agree to share this information with your primary care physician to learn about how these results are relevant to your health and/or disease risk and discuss next steps.

Research Results Acknowledgement Statement

Read and initial each statement below and sign to request your research results:

☐ I understand that test results obtained during research studies are not used for diagnostic purposes.

☐ I understand that it is my responsibility to discuss any results and follow up with my primary care physician or qualified health professional and that neither the study investigator nor research staff will provide interpretation, counseling, consultation, or care recommendations on the basis of any of the research results provided to me. I release from liability and will not hold Arizona State University or the study physician responsible if I do not promptly communicate the results of these tests to my physician.

My signature below confirms the above statements and receipt of my results from participation in the research study entitled:

_____	_____
Signature	Date
_____	
Printed Name	
_____	_____
Researcher collecting signature	Date
_____	_____
Printed Name	Phone Number

MY BLOOD PRESSURE MEASUREMENT TODAY:
DATE: _____ BP:_____

The 5 blood pressure ranges recognized by the American Heart Association are:

Blood Pressure Category	Systolic mm Hg (upper number)		Diastolic mm Hg (lower number)
NORMAL	**LESS THAN 12O**	**and**	**LESS THAN 80**
ELEVATED	**120-129**	**and**	**LESS THAN 80**
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	**130-139**	**or**	**80-89**
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	**140 OR HIGHER**	**or**	**90 OR HIGHER**
HIGH BLOOD PRESSURE (HYPERTENSION) CRISIS	**HIGHER THAN 180**	**and/or**	**HIGHER THAN 120**

We provide this as a resource.
It is important to manage your blood pressure at a healthy level.

If your blood pressure is higher than 180/120 mm Hg and you are experiencing signs of possible organ damage such as chest pain, shortness of breath, back pain, numbness/weakness, change in vision, difficulty speaking, do not wait to see if your pressure comes down on its own.

Call 9-1-1

For more information about blood pressure contact the American Heart Association:
WWW.Heart.org

Fagerström Test for Cigarette Dependence

For each statement, circle the most appropriate letter that best describes you.

1. How many cigarettes do you smoke per day?
a) 10 or less
b) 11 – 20
c) 21 – 30
d) 31 or more

2. How soon after you wake up do you smoke your first cigarette?
a) 0 – 5 min
b) 6 – 30 min
c) 31 – 60 min
d) After 60 min

3. Do you find it difficult to refrain from smoking in places where smoking is not allowed (e.g. hospitals, government offices, cinemas, libraries etc)?
a) Yes
b) No

4. Do you smoke more during the first hours after waking than during the rest of the day?
a) Yes
b) No

5. Which cigarette would you be the most unwilling to give up?
a) First in the morning
b) Any of the others

6. Do you smoke even when you are very ill?
a) Yes
b) No

Appendix 8

[Date]

RE: *VARENICLINE OTC TRIAL ON EFFICACY AND SAFETY*

Dear Doctor,

Your patient, [First Name Last Name], has expressed interest in participating in the National Institutes of Health (NIH)-funded smoking cessation study entitled ***Varenicline OTC Trial on Efficacy and Safety*** at our site [Name of Site]. This study is designed to assess the safety and efficacy of varenicline (Chantix) without healthcare provider or behavioral support.

In order to participate in the study, a signed letter of permission is required because the individual indicated they may have the following condition:

☐ History depression

Included with this form are study documents for your consideration that might help you make a decision on whether they can participate in the study.

-Copy of unsigned full Informed Consent (to be signed when/if subject has been approved [and is willing] to participate in the entire study)
-Chantix Medication Guide
-Varenicline Use and Safety Information

To be in this study, participants will receive use and safety information about varenicline as part of an approved consent form in order to make a decision about whether or not participate. If they are elgible based on IRB-approved criterion, they will be able to participate and use the study product at their discretion. All of these documents are provided to you. If participants have questions about the study medication, please refer them back to the study documents, or ask them to contact us at the number provided in the Consent form. If you have questions for us, please use the contact information on the Consent Form.

Please indicate your approval or disapproval below, and have your patient return the letter to us.

☐ I have reviewed the documents provided and **approve** my patient [First Name Last Name] to participate in the above-noted study for the following reason(s):_____

☐ I have reviewed the documents provided and **do not approve** my patient [First Name Last Name] to participate in the above-noted study for the following reason(s):_____

Physician Printed Name: _____ Physician Address: _____

Physician Signature:_____ Date:_____

Sincerely,

_____
[Printed Investigator First Name Last Name]

Appendix 9

Modified Cigarette Evaluation Questionnaire (mCEQ)*

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?

Appendix 10

Smoking Status and Resource Utilization

Smoking status

At all visits

1. Did you smoke any cigarettes, even a puff, since your last visit? Yes No
2. [If Yes to 1] Did you smoke any cigarettes, even a puff, in the last 7 days?

It has been approximately _____ weeks since your last visit.

3. On approximately how many days did you smoke? _____
4. On the days that you smoked, what is the average number of cigarettes that you smoked? ____

Resource utilization

At all visits

a. Since your last visit, which of the following additional things have you tried to reduce or quit smoking? Check all that apply.

a) A pamphlet or book
b) Individual or group counseling
c) Telephone counseling / quitline
d) Nicotine patch, gum, nasal spray, lozenge, or inhaler
e) E-cigarettes
f) Zyban / bupropion
g) Switching to chewing tobacco or snuff
h) Switching brands
i) Cutting back
j) An Internet quit smoking program
k) Alternative methods like herbs, lasers, homeopathic medicines, prayer, acupuncture, or hypnosis
l) Something else: _____

Appendix 11

Medication compliance and perceived efficacy

Medication efficacy and compliance

At all visits

5. This medication is helping me/has helped me quit smoking.

a) Strongly disagree
b) Somewhat disagree
c) Neither agree nor disagree
d) Somewhat agree
e) Strongly agree
f) Don't know

At Week 2 telephone call only

a. It has been _____days since your last visit. After the first 3 days of taking the study medication the instructions were to take 2 pills per day. Approximately what percentage of days did you take:
    i. _____two doses per day
    ii. _____one dose per day
    iii. _____no doses

At the Week 4, 8 and 12 visits

6. It has been _____ number of days since your last visit.

Approximately what percentage of days did you take:
_____two doses per day
_____one dose per day
_____no doses

Ask #7 only if any study product was reported as not used as recommended

7. Main reason for not using medication as recommended (check only one):
_____forgot
_____side effect
_____not working
_____don't need
_____other Specify:_____

At Week 12 visit only

8. Do you think you got the real drug or the placebo (fake drug) in this study?
a. Real drug
b. Placebo/fake drug
c. Don't know

Appendix 12

CHANTIX USE AND SAFETY INFORMATION
Getting Started With The Study Product (Chantix Or Placebo)

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking. The generic name is varenicline.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines. Using CHANTIX with nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more ofte than if you just use a nicotine patch alone.

What is placebo?

The placebo is a pill that contains no active medicine ingredient. The placebo pill will look identical to the CHANTIX pi will have no effect in the body.

What should I tell the study staff or check with my health care provider about before taking the Study Produc

Tell the study staff:

- any current medical problems
- all prescription and over the counter medication, vitamins and supplements you are currently taking
- If you drink alcohol
- If you are using other treatments to help you quit smoking right now

Before starting the study product, tell the study staff if you have ever had any of the health problems listed b and do not take any of the study medication unless you have discussed this with the study staff and your hea care provider.

- kidney problems or get kidney dialysis
- mental health problems
- history of seizures
- heart or blood vessel problems
- previous reactions to CHANTIX
- if you are pregnant, plan to become pregnant or breastfeeding
- history of serious allergic or skin reactions (swelling of face, tongue, neck, mouth blisters, difficulty breathing

How Do I take the Study Product?

During the first week of taking the study product, you will slowly increase the number of pills you take over 7 days as described below. After you start taking the study product, you can smoke up until your QUIT DATE. You will choose the day you want to quit. The study product will be available for 12 weeks (3 months).

You can choose a QUIT DATE in a week (7 days) or up to 30 days after starting the study product.

Your QUIT DATE has to fall between these dates: _____ and _____

If you miss a dose of the study product, take it as soon as you remember. However, if it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

If you slip up and smoke, try again. CHANTIX may work best after you take it for a few weeks.
Keep study medication out of reach of children. Store your study product at room temperature.

The study product should always be taken after eating, with a full glass of water.

STUDY PRODUCT dosing at a glance	
Days 1 – 3	Take 1 tablet each day in the morning
Days 4 - 7	Take 1 tablet in the morning and 1 in the evening
Days 8 to end of treatment	Take 1 tablet in the morning and 1 in the evening

IMPORTANT SAFETY INFORMATION AND INDICATION

When you try to quit smoking, with or without CHANTIX, you may have symptoms of nicotine withdrawal, including:

- urge to smoke
- depressed mood
- trouble sleeping
- irritability
- frustration
- anger
- feeling anxious
- difficulty concentrating
- restlessness
- decreased heart rate
- increased appetite or weight gain

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping, vivid, unusual, or strange dreams)
- constipation
- gas and/or vomiting

Some people experience new symptoms or health problems such as those indicated below.

If you experience mood or behavioral changes that are disruptive to your life, any of the health problems indicated below, or other symptoms, stop taking the study product, contact your healthcare provider and then notify the study staff.

Get emergency medical help right away if you have symptoms of a heart attack, stroke or allergic reaction.

- Some people have had new or worse mental health problems, such as changes in behavior or thinking, aggression, hostility, agitation, depressed mood, or suicidal thoughts or actions while taking or after stopping CHANTIX. These symptoms happened more often in people who had a history of mental health problems. Your family, or caregiver may be the first to notice these symptoms.
- Some people have had seizures during treatment with CHANTIX.
- New or worse heart or blood vessel problems can happen with CHANTIX.
- Sleepwalking can happen with CHANTIX, and can sometimes lead to harmful behavior.
- Do not take CHANTIX if you have had a serious allergic or skin reaction to it. These can happen with CHANTIX and can be life-threatening. This includes; swelling of the face, mouth, throat or neck; trouble breathing; rash with peeling skin, or blisters in your mouth.
- Use caution when driving or operating machinery until you know how the study medication affects you. Decrease the amount of alcohol you drink while taking the study medication until you know if the study medication affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:

- increased drunkenness (intoxication)
- unusual or sometimes aggressive behavior
- no memory of things that have happened

For additional information, contact study staff and review the consent form.

SMOKING CESSATION HELP: If you would like support to help you quit smoking, you can get free help by calling the smoking cessation quitline for your state: 1-800-QUITNOW

Revised: 1/22/18 for research purposes

Appendix 13

EMA Items for Scheduled Prompts

Items for first scheduled prompt of the day

1. How good did you sleep last night?
    a. Very bad
    b. Bad
    c. Ok
    d. Good
    e. Very good
2. Did you have any unusually vivid, realistic, or crazy dreams last night?
    a. Yes
    b. No
3. How nauseous do you feel right now?
    a. Not at all
    b. A little
    c. Somewhat
    d. A lot
    e. Extremely
4. How is your mood right now?
    a. Very bad
    b. Bad
    c. Ok
    d. Good
    e. Very good
5. How much do you want to smoke a cigarette right now?
    a. Not at all
    b. A little
    c. Somewhat
    d. A lot
    e. Very, very much

Items for the remaining scheduled prompts of the day

1. How nauseous do you feel right now?
    a. Not at all
    b. A little
    c. Somewhat
    d. A lot
    e. Extremely
2. How is your mood right now?
    a. Very bad
    b. Bad

    c. Ok
    d. Good
    e. Very good
3. How much do you want to smoke a cigarette right now?
    a. Not at all
    b. A little
    c. Somewhat
    d. A lot
    e. Very, very much

EMA Items for Evening Daily Diaries

1. How many cigarettes did you smoke today?
    a. [Drop down menu, 0-60+]
2. How many study pills did you take today?
    a. 0
    b. 1
3. Any other thoughts or feelings that you want to tell us about?
    a. [open response]

Appendix 14

MEDICATION GUIDE
CHANTIX® (CHANT-iks)
(varenicline)
Tablets

What is the most important information I should know about CHANTIX?

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including:

- urge to smoke
- depressed mood
- trouble sleeping
- irritability
- frustration
- anger
- feeling anxious
- difficulty concentrating
- restlessness
- decreased heart rate
- increased appetite
- weight gain

Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Some people have had serious side effects while taking CHANTIX to help them quit smoking, including:

New or worse mental health problems, such as changes in behavior or thinking, aggression, hostility, agitation, depressed mood, or suicidal thoughts or actions. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX. These symptoms happened more often in people who had a history of mental health problems before taking CHANTIX, than in people without a history of mental health problems.

Stop taking CHANTIX and call your healthcare provider right away if you, your family, or caregiver notice any of these symptoms. Work with your healthcare provider to decide whether you should continue to take CHANTIX. In many people, these symptoms went away after stopping CHANTIX, but in some people symptoms continued after stopping CHANTIX. It is important for you to follow-up with your healthcare provider until your symptoms go away.

Before taking CHANTIX, tell your healthcare provider if you have ever had depression or other mental health problems. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines.

Who should not take CHANTIX?

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

- swelling of the face, mouth (tongue, lips, gums), throat or neck
- trouble breathing
- rash, with peeling skin
- blisters in your mouth

What should I tell my healthcare provider before taking CHANTIX?

See "What is the most important information I should know about CHANTIX?"

Before you take CHANTIX, tell your healthcare provider if you:

- use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch

alone.

- have kidney problems or get kidney dialysis. Your healthcare provider may prescribe a lower dose of CHANTIX for you.
- have a history of seizures
- drink alcohol
- have heart or blood vessel problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
- are breastfeeding. It is not known if CHANTIX passes into breast milk. If you breastfeed and take CHANTIX, monitor your baby for seizures as well as spitting up or vomiting more than normal.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your healthcare provider may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your healthcare provider if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CHANTIX?

- There are 3 ways that you can use CHANTIX to help you quit smoking. Talk to your healthcare provider about the following 3 ways to use CHANTIX:
  - Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. Take CHANTIX for 12 weeks.
    OR
  - Start taking CHANTIX before you choose a **quit date.** Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHANTIX for 12 weeks.
    OR
  - If you are sure that you are not able or willing to quit smoking right away, start taking CHANTIX and reduce smoking during the first 12 weeks of treatment, as follows:

Weeks 1 through 4	Reduce your smoking to reach one-half of your starting daily number of cigarettes. Example: If you usually smoke 20 cigarettes each day, reduce your smoking to 10 cigarettes each day during weeks 1 through 4.
Weeks 5 through 8	Reduce your smoking to reach one-quarter of your starting daily number of cigarettes. Example: If you usually smoked 20 cigarettes each day, reduce your smoking to 5 cigarettes each day during weeks 5 through 8.
Weeks 9 through 12	Keep reducing your smoking until you are no longer smoking (you reach zero cigarettes each day).

Aim to quit by the end of the 12th week of treatment, or sooner if you feel ready. Continue to take CHANTIX for another 12 weeks, for a total of 24 weeks of treatment.

Starting CHANTIX before your **quit date** gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your healthcare provider.

- CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

Day 1 to Day 3	○ White tablet (0.5 mg) ○ Take 1 tablet each day

Day 4 to Day 7	○ White tablet (0.5 mg) Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	○ Blue tablet (1 mg) ○ Take 1 in the morning and 1 in the evening

- Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
- Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your healthcare provider may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.
- Take CHANTIX after eating and with a full glass (8 ounces) of water.
- This dosing schedule may not be right for everyone. Talk to your healthcare provider if you are having side effects such as nausea, strange dreams, or sleep problems. Your healthcare provider may want to reduce your dose.
- If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

What should I avoid while taking CHANTIX?

- Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.
- Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:

  - increased drunkenness (intoxication)
  - unusual or sometimes aggressive behavior
  - no memory of things that have happened

What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- **See "What is the most important information I should know about CHANTIX?"**
- **Seizures**. Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.
- **New or worse heart or blood vessel (cardiovascular) problems**, mostly in people, who already have cardiovascular problems. Tell your healthcare provider if you have any changes in symptoms during treatment with CHANTIX.
  Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:
  - chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
  - pain or discomfort in one or both arms, back, neck, jaw or stomach
  - shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- **Sleepwalking** can happen with CHANTIX, and can sometimes lead to behavior that is harmful to you or other people, or to property. Stop taking CHANTIX and tell your healthcare provider if you start sleepwalking.
- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.

- **Serious skin reactions**, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- swelling of the face, mouth (tongue, lips, and gums), throat or neck
- trouble breathing
- rash with peeling skin
- blisters in your mouth

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your healthcare provider about side effects that bother you or that do not go away.
These are not all the side effects of CHANTIX. Ask your healthcare provider or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep CHANTIX and all medicines out of the reach of children.**

General information about the safe and effective use of CHANTIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CHANTIX that is written for healthcare professionals.
For more information about CHANTIX and tips on how to quit smoking, go to www.CHANTIX.com or call 1-877-242-6849.
If you are motivated to quit smoking and did not succeed during prior CHANTIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your healthcare provider about whether another course of CHANTIX therapy may be right for you.

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate
Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

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Appendix #15

Suicidal Behaviors Questionnaire-Revised (SBQ-R)

The Suicidal Behaviors Questionnaire-Revised (SBQ-R) provides a broad range of information in a brief administration. Responses can be used to identify at-risk individuals and specific risk behaviors. This questionnaire must be completed by all potential study subjects during screening. A score ≥7 indicates potential for suicidal ideation and would confirm study exclusion criteria #6. Copies of this questionnaire and details for interpretation and scoring will be provided in the study Procedure Manual and completed questionnaires must be present as source documents. Any subject meeting this exclusion must be followed by the clinical site according to site policies.

1. **Have you ever thought about or attempted to kill yourself?** (check one only)
   - □ 1. Never
   - □ 2. It was just a brief passing thought
   - □ 3a. I have had a plan at least once to kill myself but did not try to do it
   - □ 3b. I have had a plan at least once to kill myself and really wanted to die
   - □ 4a. I have attempted to kill myself, but did not want to die
   - □ 4b. I have attempted to kill myself, and really hoped to die
2. **How often have you thought about killing yourself in the past year?** (check one only)
   - □ 1. Never
   - □ 2. Rarely (1 time)
   - □ 3. Sometimes (2 times)
   - □ 4. Often (3-4 times)
   - □ 5. Very Often (5 or more times)
3. **Have you ever told someone that you were going to commit suicide, or that you might do it**? (check one only)
   - □ 1. No
   - □ 2a. Yes, at one time, but did not really want to die
   - □ 2b. Yes, at one time, and really wanted to die
   - □ 3a. Yes, more than once, but did not want to do it
   - □ 3b. Yes, more than once, and really wanted to do it
4. **How likely is it that you will attempt suicide someday?** (check one only)
   - □ 0. Never
   - □ 1. No chance at all
   - □ 2. Rather unlikely
   - □ 3. Unlikely
   - □ 4. Likely
   - □ 5. Rather likely
   - □ 6. Very likely