GENETICALLY INFORMED SMOKING CESSATION TRIAL

STUDY PROTOCOL

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A Introduction

A1 Study Abstract

This is a randomized controlled trial examining the effects of one experimental factor (combination Nicotine Replacement Therapy (NRT) vs. varenicline vs. placebo for 3 months) and one non-experimental participant characteristic: CHRNA5 genotypes associated with high, intermediate, and low risk levels for nicotine dependence and smoking cessation failure. Based on the frequency distribution of these genotypes, there will be sufficient numbers of each genetic group represented in the active and placebo arm. All patients will receive intensive smoking cessation counseling. We will examine the main effects of medication (combination NRT vs. varenicline vs. placebo) and genotype (high, intermediate, and low risk), as well as the pharmacogenetic interaction between genotype and medication on the primary cessation outcome (abstinence at end of treatment, ABST_EOT) and other outcomes (abstinence at 6 months). We chose the primary efficacy measure of abstinence at 3 months (EOT) because preliminary data (Chen et al., 2012) suggest the genetic effects on cessation take place in the early cessation stage. Our hypothesis is that NRT significantly increases smoking abstinence in patients possessing high-risk haplotypes, but not amongst patients without such haplotypes.

This experiment will answer the following questions:
1) Is there a genotype X Pharmacotherapy (cNRT vs. placebo) interaction with regard to abstinence?
2) Is there a genotype X Pharmacotherapy (varenicline vs. placebo) interaction with regard to abstinence?

This study has been designed following the guidelines and recommendations for conducting and reporting the results of clinical trials as described in the CONSORT (Consolidated Standards of Reporting Trials) statement. In addition, the design and methodology of the study are consistent with current guidelines and recommendations provided by the clinical trial experts in smoking cessation (Society for Research on Nicotine and Tobacco recommendations for follow-up procedures).

A2 Primary Hypothesis

Hypothesis #1 is to examine whether medication effect (cNRT vs. placebo) varies with CHRNA5 (i.e. a genotype X medication interaction). A series of logistic regression models will be used to examine main effects of genotype (rs16969968) and medication before testing genotype x medication interactions, with sex, age, and study cohort as covariates using logistic regression models.

Hypothesis #2 is to examine whether medication effect (varenicline vs. placebo) varies with CHRNA5 (i.e. a genotype X medication interaction). A series of logistic regression models will be used to examine main effects of genotype (rs16969968) and medication before testing genotype x medication interactions, with sex, age, and study cohort as covariates using logistic regression models.

A3 Purpose of the Study Protocol

This experiment will answer the following questions:
1) Is there a genotype X Pharmacotherapy (cNRT vs. placebo) interaction with regard to abstinence?
2) Is there a genotype X Pharmacotherapy (varenicline vs. placebo) interaction with regard to abstinence?

B Background

B1 Prior Literature and Studies

In a general population sample of smokers seeking to quit, we recently discovered that genetic markers in the CHRNA5 gene predict cessation success and response to pharmacotherapy. Patients with the high-risk variants had a 3-fold enhanced response to pharmacotherapy as compared to those with the low-risk and intermediate-risk variants. This information can be used to separate patients who are at serious risk of smoking relapse without pharmacotherapy from those who are likely to be able to quit on their own and thus not benefit from the medication (Chen et al, 2012). These results have been replicated in the large Pharmacogenetics of Nicotine Addiction Treatment (PNAT) consortium (Bergen et al, 2012). To address the current barriers to pharmacotherapy use which lead to failed smoking cessation in these patients, this genetically informed treatment study will investigate how genetic information can be used to personalize cessation pharmacotherapy to maximize efficacy for patients.

B2 Rationale for this Study

Our overarching goal is to identify the most appropriate genetically informed smoking cessation treatments for smokers hoping to quit.

Our recent finding suggests that the effect of pharmacotherapy on cessation varies with genotype (nicotinic receptor gene, *CHRNA5*): pharmacotherapy significantly increases abstinence amongst individuals with the high-risk genetic variants, but provides little benefit to individuals with the low-risk variants. The genotype is useful to predict relapses and response to medication (Chen et al, 2012). Weighing both risk and efficacy on cessation success we will identify smokers who are more likely to relapse, and need pharmacotherapy in order to attain optimal outcomes versus those who will receive little benefit from pharmacotherapy. This work can lead to personalized treatment that promotes long term cessation success by focusing pharmacotherapy use on those who can benefit from it.

C Study Objectives

C1 Primary Aim

Specific Aim 1: To recruit 822 participants who are active smokers in a smoking cessation trial. All patients will be randomized to combination NRT (Nicotine Replacement Therapy) with nicotine patch and lozenge, or varenicline, or placebo for 3 months. All patients will receive intensive smoking counseling. These patients will be assessed in person at baseline, 3 months (if biochemical verification of abstinence is needed), 6 months (if biochemical verification of abstinence is needed), and by telephone at the last day pre-quit, quit date, 1 week, 2 weeks, 4 weeks, 3 months (if biochemical verification of abstinence is not needed), 6 months (if biochemical verification of abstinence is not needed) and 1 year after the quit date.

Specific Aim 2: To determine if the effect of cessation pharmacotherapy (combination Nicotine Replacement Therapy (NRT) vs. varenicline vs. placebo for 3 months) on abstinence varies significantly with genotype. We will examine the association between two genetic variants in the CHRNA5 gene and treatment on smoking cessation success (abstinence at end of treatment (ABST_EOT)). We will test the main effects of pharmacotherapy and genotype, as well as the interaction between them. Secondary cessation outcomes include abstinence at 6 months and 1 year.

C2 Secondary Aim

To study the effect of other genetic or environmental risk factors on smoking cessation in this population.

C3 Rationale for the Selection of Outcome Measures

We will conduct a randomized controlled smoking cessation trial of 822 participants to examine the association between the genetic variants (*CHRNA5),* treatment, and cessation success (abstinence at end of treatment (ABST_EOT)). We will evaluate secondary cessation outcomes (abstinence at 6 months and 1 year).

Primary Outcome Measure: 7-day point prevalence abstinence [Time Frame: Week 12]
The definition of this measure requires: (a) no self-reported smoking (not even a puff of a cigarette) for at least the 7 days prior to the assessment, and (b) CO biochemical verification of abstinence.

Secondary Outcome Measures: Continuous Abstinence (11 weeks) [Time Frame: 12 weeks with the first 1 week initial grace period]
The definition of this measure requires: Not taking even 1 cigarette puff from target quit date to end of treatment with the first 1 week initial grace period.

7-day point prevalence quit rate [Time Frame: Week 24]
The definition of this measure requires: (a) no self-reported smoking (not even a puff of a cigarette) for at least the 7 days prior to the assessment, and (b) biochemical verification of abstinence.

Number of days to lapse and relapse [Time Frame: Assessed from the target quit day through 52 weeks.]
The number of days to lapse is defined as the number of days from the target quit date until the participant reports smoking (even a single puff). The number of days to relapse is defined as the number of days from the target quit day until the first of seven consecutive days of smoking.

Initial Cessation [Time Frame: Assessed for the first seven days after the target quit date.]
Defined as at least 1 day of abstinence during the first 7 days after the target quit day.

Longitudinal models of abstinence outcomes across multiple time points [Time Frame: 0-52 Weeks]
The definition of this measure requires; no self-reported smoking (not even a puff of a cigarette) for at least 7 days prior to the assessment.

Longitudinal models of smoking quantity in cigarettes per day outcomes across multiple time points. [Time Frame: 0-52 Weeks]The definition of this measure requires self-reported cigarettes per day.

Medication adherence [Time Frame: Pre-quit week to Week 12]Adherence is the proportion of expected medication (varenicline, patch, lozenge) taken as advised during pre-quit week to week 12
Side effects [Time Frame: Pre-quit week to Week 12]
All reported side effects (occurring>4%) will be summarized and presented for the study. In addition, the investigators will further identify a pre-specified set of key side effects as being related to drug agonist effects (e.g., nausea, vomiting, racing heart, headache, and sleep disturbance). These will be analyzed as rate of occurrence during the period of medication use.

Withdrawal [Time Frame: Pre-quit week to Week 4]
Withdrawal severity is assessed by Wisconsin Smoking Withdrawal Scale (WSWS) overall withdrawal scores, craving, and negative affect scores.

D Study Design

D1 Overview or Design Summary

This is a rs16969968 based stratified randomized controlled trial design examining the effects of one experimental factor (combination NRT vs. varenicline vs. placebo for 3 months) and one non-experimental participant characteristic: *CHRNA5* genotypes associated with high, intermediate, and low risk levels for nicotine dependence and cessation failure. Based on the frequency distribution of these genotypes, there will be sufficient numbers of each genetic groups represented in the active and placebo arm. We will examine the main effects of medication (cNRT vs placebo as well as varenicline vs. placebo) and genotypes (high, intermediate, and low risk), as well as the pharmacogenetic interaction between the genotypes and medication on the primary cessation outcome (abstinence at end of treatment, ABST_EOT) and other outcomes (abstinence at 6 months and 1 year). We choose the primary efficacy measure of abstinence at 3 month (EOT) because our preliminary data from the UW-TTURC trial suggest the genetic effects on cessation take place in the early cessation stage. Our hypothesis is that NRT significantly increases smoking abstinence in patients possessing high-risk genotypes, but not amongst patients without such genotypes.

This experiment will achieve Aims 1 and 2 by answering the following questions:

1) Is there a genotype X Pharmacotherapy (cNRT vs. placebo) interaction with regard to abstinence?
2) Is there a genotype X Pharmacotherapy (varenicline vs. placebo) interaction with regard to abstinence?

D2 Subject Selection and Withdrawal

Some subjects for this study have participated in the previous study: the Collaborative Genetic Study of Nicotine Dependence (COGEND). Subjects who participated in COGEND must have provided a DNA sample. Subjects must have given permission to share data and to be contacted for future studies for both COGEND. Subjects must have active nicotine dependence. We are expanding enrollment opportunities to the community, by recruiting from the volunteers for health program, and smokers interested in smoking cessation in the local community. These participants must give permission to share data. When participants agree to be part of this study he/she gives up any property rights he/she may have in the blood and data. Cells from the blood will be used to develop cell lines. DNA and plasma will then be extracted from these cell lines and used for research purposes. We will use the blood sample (DNA, plasma, cell lines from blood), and data for other research projects in the future.

2.a Inclusion Criteria

Inclusion:
1) Adult (>=21 years of age), seeking treatment for smoking cessation.
2) Able to speak English,
3) Active smoking (Cigarettes Per Day (CPD) >=5) and **exhaled CO >=8 ppm**
4) Agree to participate in this randomized smoking cessation trial with follow up assessments up to 12 months, and

2.a Exclusion Criteria

Exclusion:

The subject will be excluded for having a condition that prevents him/her from effectively participating in the protocol.
1) Pregnancy or breast feeding,
2) Active use or recent use (<= to 1 month) of medication or e-cigarettes for nicotine dependence/smoking cessation, or use of e-cigarettes for more than 9 days in the prior month
3) Allergy to Nicotine patch, Nicotine lozenge, or varenicline
4) Unwillingness to prevent pregnancy during the medication phase and 1 month afterwards (women only),
5) Significant cardiac conditions (myocardial infarction (heart attack), unstable angina, coronary angioplasty, cardiac bypass) or serious arrhythmia within 6 months
6) Current heavy alcohol consumption (greater than or equal to 6 drinks/day, 6 days/week)
7) Active psychosis or poorly controlled depression in the past 6 months
8) Any suicide attempt or poorly controlled depression in the past 6 months,
9) End stage renal disease with hemodialysis

2.b Ethical Considerations

This study will recruit from all eligible subjects regardless of their age, gender, and ethnicity. No children or pregnant women will be included in this study.

2.c Subject Recruitment Plans and Consent Process

We propose to enroll previous participants of the COGEND study, VFH, and the local community. We expect we can successfully recruit 822 patients in 3 years.

Step 1. Screening of Potentially Eligible Subjects

The PI or research assistant will need to access the following data element.

1) Subject agreed to be contacted to participate in a smoking cessation trial.

Step 2. Ask the potential participant the following screening questions to determine eligibility.

1) How many cigarettes do you smoke a day?
2) Are you committed to participating in this study on treatment for smoking cessation for a full year?
3) Are you willing to use birth control for 3 months while you are receiving medication treatment for smoking cessation and one month after? (ONLY for pre-menopausal women)
4) Are you pregnant or breast feeding? (ONLY for pre-menopausal women)
5) Do you currently take the medication Bupropion, Wellbutrin, Zyban, Varenicline, or Chantix, or nicotine patch or lozenge?
6) Are you allergic to the Nicotine Patch, lozenge, or varenicline?
7) Did you have significant cardiac conditions (an acute heart attack, unstable angina, coronary angioplasty, cardiac bypass) in the past 6 months?
8) Do you currently drink alcohol at the level of at least 6 drinks per day, 6 days per week?

9) Have you had active depression or psychosis in the past 6 months?
10) Do you currently have thoughts of suicide or have a suicide attempt in the past 6 months?
11) Do you have end stage kidney disease requiring hemodialysis?

Step 3. Smoking Verification

Patients will complete a carbon monoxide (CO) breath test. A cut-off level of >=8 ppm will be used to verify self-reported smoking.

Step 4. Obtain Informed Consent

Patients who express interest in participating will be informed in greater detail about the study and receive screening for eligibility criteria by the PI psychiatrist or the research assistant. The patients will learn about general requirements for participation (e.g., need for follow-up, participation in assessments, etc.) as well as risks associated with nicotine toxicity, nicotine withdrawal, blood sample and pharmacotherapy. If still interested and eligible, the patients will then be asked to provide written informed consent to participate, on a form approved by the Washington University School of Medicine Institutional Review Board. Study candidates will read the informed consent document and be given an opportunity to ask any questions regarding study participation. They will also complete the consent form. A follow up contact can be scheduled if potential participants would like to have more time to consider participation. Participants will receive a signed copy of the consent document.

2.d Randomization Method and Blinding

The participants will be randomized with the ratio 1:1:1 to the treatment arm of combination NRT (nicotine patch and lozenge) plus smoking cessation counseling, or the treatment arm of varenicline plus smoking cessation counseling, or the treatment arm of placebo (patch and lozenge or pill) plus smoking cessation counseling.

Participants will be randomly assigned to 1) combination NRT plus counseling, 2) varenicline plus counseling, or 3) placebo plus counseling. SAS Version 9 statistical software will be used to generate the random assignment table stratified by CHRNA5 genotype rs16969968. The group assignment and genotype will be coded to ensure that the double blind is maintained, and the interface will prevent staff from having access to the participant's assignment and genotype until after the baseline and post treatment assessments have been completed.

2.e Risks and Benefits

Risks associated with this research are judged to be minimal.

Smoking withdrawal is associated with a number of unpleasant symptoms such as sleep disturbance, hunger, craving, and negative mood. Most smokers have tried to quit in the past and are familiar with these phenomena.

With respect to the pharmacotherapy, participants will be made aware of the common side effects before they consent to participate in the study. It should be noted that the nicotine patch and lozenge are available over the counter. The nicotine patch has very few side effects, but participants may have a local skin reaction, and rarely, individuals may have a more systematic

allergic reaction. The most common side-effects associated with the nicotine patch are diarrhea, indigestion, nausea and vomiting, dry mouth, muscle and joint pain, sleeplessness, and abnormal dreams. Side effects associated with wearing an adhesive patch include skin rash, redness, and itching or irritation of the skin. The most likely side effects associated with the nicotine lozenge are heart burn, hiccup, nausea, upper respiratory track infection, coughing, and sore throat. In most cases, these side effects have been mild to moderate in intensity and go away once the patch is removed. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible.

Varenicline is approved by the FDA for smoking cessation and is medically safe for most smokers except for individuals with severe (end stage) kidney failure or hypersensitivity to varenicline. In addition, although no causal relationship has been established, current labeling for varenicline (FDA, 2011) recommends monitoring for serious neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. Varenicline labeling also notes that some individuals with pre-existing psychiatric conditions may experience worsening of their conditions. Preliminary data from the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) smoking cessation trials showed comparable rates of discontinuation and adverse events due to NRT and varenicline. The low rate of serious adverse events is consistent with recent data on the safety of varenicline.

Blood draw may result in bruising, and very rarely, infection at the site of needle stick.

Some patients may experience emotional distress during evaluations for depression and anxiety.

Finally patient confidentiality would be compromised if unauthorized individuals were to establish the identity of any participant.

What is done to minimize the risks?

The principal investigator psychiatrist will be responsible for routine monitoring of unanticipated health events. This monitoring includes scheduled monthly meetings and review of written documentation. Unanticipated health event assessment, recording, reporting, and investigation will be accomplished through structured/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The principal investigator has ultimate responsibility for ensuring that unanticipated health events are detected and reported in a timely manner. Health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity, significant change in mood, suicidal ideation) will be immediately reported to the study physician who will determine an appropriate course of action.

Potential side effects of combination NRT (patch and lozenge) will be closely monitored. The transdermal NRT is chosen for testing in participants for these safety reasons:

1) Transdermal NRT has slower absorption, lower peak serum level, and fewer cardiovascular effects, vs. varencline, which has an FDA warning on use with cardiac patients
2) NRT is the most commonly used cessation medication in post-MI patients
3) Fewer drug interactions (vs. bupropion, which has an unsafe interaction with an MAO inhibitor if the patient is depressed).

Study participants will be closely monitored in accordance with current FDA recommendations as well as the consensus recommendations of the 2008 Guideline Panel which provides additional detailed instructions for clinicians regarding all FDA approved smoking cessation medications. We will follow the patient instruction and adverse events monitoring procedures used in the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI). Patient education about possible side effects, access to a medication hotline, and ongoing monitoring will be consistent with FDA recommendations, clinical practice guidelines, and procedures successfully used in prior and ongoing UW-CTRI research using varenicline and combination NRT. This protocol is consistent with the 2010 FDA warning and recommendations for monitoring requirements regarding the black box warning of psychiatric risk for varenicline. In addition, we will make appropriate changes in study procedures if the FDA issues updates on varenicline.

All medical information and data from the interviews will be kept in a locked file cabinet in a locked office and identified by a code number. The master list of subject names will be kept in a separate locked file cabinet in a separate locked office by the Principal Investigator. Computerized research data are identified only by subject identification numbers and codes, and confidential data files are password protected. Written records of counseling sessions and audio recordings of sessions will be kept in a locked cabinet and will be destroyed within one year of the termination of the project. Audio recordings will be obtained if authorized by the participant. Only authorized individuals will be permitted to review these records. We have followed these procedures in the past without any breeches of confidentiality, and we feel certain that we will be able to maintain the same level of security for this project.

BENEFITS

The potential benefits for smokers participating in this study include the chance to receive free smoking cessation counseling and pharmacotherapy, both of which double a smoker's odds of quitting.

In addition, this research has the potential to provide improved treatment strategies for clinicians trying to help patients quit smoking. This could result in more efficient provision of a maximally effective intervention for smokers.

The proposed research will test combination NRT and varenicilne in patients with different genetic markers and identify effective pharmacotherapy according to the genetic markers. The results from this study will allow researchers to determine which smoker subgroups will benefit from pharmacotherapy and which smoker subgroups will not. This should contribute to the improvement of standard clinical care of such patients, and may result in improved medical outcomes. Given the limited risks of NRT and varenicilne, and the limited adverse effects, we believe that the potential risks involved in participating in the study are outweighed by the benefits to both society and the individual.

2.f Early Withdrawal of Subjects

Once enrolled, follow-up protocols will assess the presence of medication side effects and

unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alternations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects once they begin medication treatment.

Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

2.g When and How to Withdraw Subjects

We are conducting this research with strong safety measures in place (close monitoring and screening) to gather the needed data without imposing unacceptable risks. The participants will remain under the care of their own physician(s) throughout the study. To facilitate safety, participants who are not medically appropriate to take combination NRT or varenicline will not be included in the study (see exclusion criteria). Once enrolled, follow-up protocols will assess the presence of medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alternations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects once they begin medication treatment. We will refer patients to the study physician as needed.

Participants' medications will be continued if they have relapsed to smoking regularly. Subjects with symptoms of nicotine toxicity (including diarrhea, abdominal pain, vomiting, dizziness, and headache) reported at any research contact will be told to discontinue their medication immediately until they have a chance to discuss their symptoms with the study physician (Dr. Chen) or their primary care doctor, who will decide upon a course of action based upon the patient's status and risk (e.g., a dose reduction or medication discontinuation). Emergency care will be administered as needed. If the only severe symptom is sleep disturbance, subjects will be instructed to remove the patch at night, but otherwise keep receiving treatment according to the protocol. Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

Any patient who reports discomfort as a result of completing the assessment of depression and anxiety will be reminded that the evaluation is discretionary, that it will be discontinued if the patient wishes, and that doing so will not affect the patient's medical care. The experienced psychiatrist investigator will be on call in case a patient has an adverse reaction to a screening or outcome evaluation. We have administered these tests to over 2,500 patients without a single subject reporting more than mild, transient emotional distress.

2.h Data Collection and Follow-up for Withdrawn Subjects

For subjects who have withdrawn from the study treatment, and given consent for us to follow up, we will collect data on their basic smoking status, and adverse effects.

D3 Study Drug

3.a Description

The participants will be randomized with the ratio 1:1:1 to the treatment arm of combination NRT (nicotine patch and lozenge) plus smoking cessation counseling, the treatment arm of varenicline plus counseling, or to the treatment arm of placebo (patch and lozenge or pill) plus smoking cessation counseling.

3.b Treatment Regimen

During the baseline visit (visit 1), all participants will be randomized at 1:1:1 to 1) one arm of combination nicotine and smoking cessation counseling, or 2) varenicline and smoking cessation counseling, and 3) another arm of placebo and smoking cessation counseling at no cost to participants. Participants will receive enough patches to last 12 weeks. The duration of medication treatment is 12 weeks (standard for participants who smoke >9 cigs/day=8 weeks of 21mg, 2 weeks of 14mg, and 2 weeks of 7mg nicotine patches; standard for participants who smoke 5-9 cigs/day=8 weeks of 14mg and 4 weeks of 7mg;).

Nicotine Lozenge: The 4 mg dosage is recommended for patients who take their first cigarette within 30 minutes of waking and the 2mg dosage is recommended for patients who take their first cigarette more than 30 minutes after waking. Participants will begin taking lozenges a week before abstinence to replace some cigarettes. Participants will then take 1 lozenge every 1-2 hours for 6 weeks, then 1 lozenge every 2-4 hours for 3 weeks, and 1 lozenge for every 4-8 hours for 3 weeks. Participants will be encouraged to take a minimum of 4 pieces/day unless this amount produces adverse effects.

Varenicline: Varenicline will be initiated with a titration for 7 days before the quit date. Before the quit date, participants will take one 0.5mg tablet daily for 3 days, then two 0.5mg tablets for 4 days (one in the morning and one in the evening). After the quit date (day 8), participants will take 1mg tablet in the morning and in the evening.

Placebo: 50% of participants assigned to the placebo group will receive placebo patch/lozenge, and 50% will receive the placebo pill as a control for the two active medication arms.

All participants will be given complete instructions on proper medication use, and will be urged to contact his/her physician and a study hotline number immediately in case of listed symptoms of nicotine toxicity or side effects. Dose changes or discontinuation of NRT may be recommended; all changes will be addressed in analyses of adherence outcomes.

3.c Method for Assigning Subjects to Treatment Groups

The participants will be randomized with the ratio 1:1:1 to one treatment arm of combination NRT plus smoking cessation counseling, one treatment arm of varenicline plus counseling, or to placebo plus smoking cessation counseling.

Participants will be randomly assigned to each of the 3 arms. SAS Version 9 statistical software will be used to generate the random assignment table. The group assignment will be coded to ensure that the double blind is maintained, and the interface will prevent staff from having

access to the participant's assignment until after the baseline and post treatment assessments have been completed. Adequacy of blinding will be tested and different raters will assess efficacy vs. safety to ensure blinding.

3.d Preparation and Administration of Study Drug

During the baseline visit (visit 1), all participants will be randomized at 1:1:1 to each of the 3 arms described above and receive treatments at no cost to participants.

3.e Subject Compliance Monitoring

Subjects will be asked to report their use of medication in each follow up visit during the 3 month medication treatment period.

3.f Prior and Concomitant Therapy

Subjects currently taking the medication Bupropion, Wellbutrin, Zyban, will be excluded.

Non-Study Treatment: Patients will be asked to refrain from non-study smoking cessation interventions such as intensive smoking cessation counseling and smoking cessation medication during treatment. Non-Study Treatment data will be assessed at each follow up visit to document whether the patient is receiving any non-study treatment for smoking cessation or other medical conditions, including medications, counseling, quit line, support groups, self-help books, and complementary/ alternative medicine remedies.

3.g Packaging

The study medication (Nicotine patch and place patch, varenciline, and placebo (patch and lozenge or pill) will have identical packaging when they are provided to the participants.

3.h Blinding of Study Drug

The group assignment will be coded to ensure that the double blind is maintained, and the interface will prevent staff from having access to the participant's assignment until after the baseline and post treatment assessments have been completed.

3.i Receiving, Storage, Dispensing and Return

Participants will receive their study medication when they attend the in office visit 1 (baseline).

E Study Procedures

E1 Screening for Eligibility

We propose to enroll previous participants of the COGEND study and the GERS study and to expand enrollment opportunities to the community, by recruiting from the volunteers for health program in our University Hospital System, and smokers interested in smoking cessation in the local community. We expect we can successfully recruit 822 patients in 3 years.

Step 1. Screening of Potentially Eligible Subjects

The PI or research assistant will need to access the following data element.

1) Subject agreed to be contacted to participate in a smoking cessation trial.

Step 2. Ask the potential participant the following screening questions to determine eligibility.

1) How many cigarettes do you smoke a day?
2) Are you committed to participating in this study on treatment for smoking cessation for a full year?
3) Are you willing to use birth control for 2 months while you are receiving medication treatment for smoking cessation? (ONLY for pre-menopausal women)
4) Are you pregnant or breast feeding? (ONLY for pre-menopausal women)
5) Do you currently take the medication Bupropion, Wellbutrin, Zyban, Varenicline, or Chantix?
6) Are you allergic to the Nicotine Patch, lozenge, or varenicline?
7) Have you had significant cardiac conditions (heart attack, unstable angina, coronary angioplasty, cardiac bypass) in the past 6 months?
8) Do you currently drink alcohol at the level of at least 6 drinks/day, 6 days/week?
9) Have you had active depression or psychosis in the past 12 months?
10) Do you currently have thoughts of suicide or have a prior suicide attempt in the past 12 months?
11) Do you have end stage kidney disease requiring hemodialysis?

Step 3. Obtain Informed Consent

Patients who express interest in participating will be informed in greater detail about the study and receive screening for eligibility criteria by the PI psychiatrist or the research assistant. The patients will learn about general requirements for participation (e.g., need for follow-up, participation in assessments, etc.) as well as risks associated with nicotine toxicity, nicotine withdrawal, blood draw, and pharmacotherapy. If still interested and eligible, the patients will then be asked to provide written informed consent to participate, on a form approved by the Washington University School of Medicine Institutional Review Board. Study candidates will read the informed consent document and be given an opportunity to ask any questions regarding study participation. They will also complete the HIPAA form and the consent form. A

follow up contact can be scheduled if potential participants would like to have more time to consider participation. Participants will receive a signed copy of the consent document.

E2 Schedule of Measurements

Participants will receive a baseline assessment of smoking history and withdrawal symptoms, provide a breath sample for alveolar CO level, provide blood sample for assessments of nicotine metabolism and genetic markers, receive smoking cessation counseling, and be randomized to one of two groups (transdermal nicotine replacement therapy and counseling vs placebo and counseling). These evaluations will be conducted by the Principal Investigator Dr. Chen or a research assistant. The baseline assessment will take approximately 90 minutes. Participants will be asked to also participate in 8 follow up visits, two in person at 3 months (if biochemical verification is needed) and 6 months (if biochemical verification is needed) and the rest by phone at the last pre-quit, quit date, 1 week, 2 weeks, 4 weeks, 3 months (if biochemical verification is not needed), 6 months (if biochemical verification is not needed) and 1 year after the quit date.

	office	office	phone	phone	phone	phone	phone	office/phone	office/phone	phone
Reimbursement	$25	$25/$40	N/A	N/A	N/A	N/A	N/A	$40/$20	$40/$20	$10
Visit Number	Pre- Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Visit description	Initial Visit	Baseline	pre-quit	quit day	wk 1 post quit	wk2 post quit	wk4 post quit	wk12 post quit	wk26 post quit	wk52 post quit
IF GENOTYPE DATA IS NEEDED										
Blood Sample	X									
SSAND	X									
Realm-R	X									
Measurement of expired breath CO	X									
ASSESSMENTS										
Screening Questions at Baseline (before consent)		X								
Contact Information Form		X								
Baseline Assessment (Demographics/smoking status/Tobacco History/ Environmental History/ Brief Medical history)		X								
Brief WISDM37		X								
Measurement of expired breath CO		X						X**	X**	
WSWS		X	X*	X	X*	X*	X*	X	X*	X*
Adverse Event Assessment		X	X*	X*	X*	X*	X*	X		
Follow-up Assessment (smoking status, Timeline follow back, enviromental factors)			X	X	X	X	X	X	X	X
Pill/Medicine Count								X		
Expectations								X		
Adherence self reported			X	X	X	X	X	X		
INTERVENTION COMPONENTS										
Approximate Counseling (minutes)		15	10	10	10	10	10	10		
Medication (cNRT, varenicline, placebo)		X	X	X	X	X	X	X		
Blood Sample- if pre-visit was not needed		X								
*indicates a brief version of assessment; **If self-reported abstinence CO data for biochemical confirmation										

E3 Initial Visit and Visit 1

Initial Visit (if needed)
Participants recruited from the community or volunteer for health will have a two hour initial visit to provide a blood sample for genetic analysis, and ask questions about health, use of alcohol and drugs, personality and family smoking history, and a carbon monoxide breath test.

The initial visit if needed for the genetic data will take approximately two hours and includes the following:
Blood sample
Realm-R

Semi Structured Assessment of Nicotine Dependence – Short Version (SSAND)
Alveolar CO level

Visit 1:
At the next visit (visit 1), participants will receive a baseline assessment of smoking history and withdrawal symptoms. This visit will take approximately 90 minutes.

The baseline assessment includes the following:
Demographics
Smoking history
Medical history
Environmental factors
Beck Depression Inventory (BDI)
Beck Anxiety Inventory (BAI)
Alveolar CO level
Contact Information Sheet
Adverse Events Screener
Brief WISDM 37
WSWS

They will receive baseline cessation counseling, being randomized to nicotine or placebo patches or varenicline or placebo along an instruction sheet, and set a quit date.

E4 Visit 2-9

At Follow up visits at the last day pre-quit, quit date, 1 week, 2 weeks, 4 weeks, 3 months, 6 months, and 1 year after the quit date, administer follow up assessments.

At follow up visits, all participants will receive the follow up visit assessment.

The follow up assessment by phone includes the following:
Smoking Status
Non-study treatment data
Patch/Lozenge/Pill use and potential side effects
Adherence
Medical History
Environmental factors
Adverse Events Screener
WSWS

At the in-office follow up visits at 12 weeks and 6 months post-quit, the subject will provide a breath sample for alveolar CO level.

In follow visits up to 12 weeks after quit date, subjects receive smoking cessation counseling. This session will be the final counseling session.

4.a Safety and Compliance Monitoring

This study has a Data Safety and Monitoring Plan (DSMP), and a Data and Safety Monitoring Board (DSMB).

The Individual Patient Safety Committee (IPSC) will include the study's key personnel: Li-Shiun Chen, M.D., M.P.H., Sc.D., a psychiatrist; Robert Carney, Ph.D., a psychologist; Laura Bierut, M.D., a psychiatrist; The IPSC will review monthly reports on all participants. The IPSC will be blinded to the patient's group assignment.

In addition, we have a Data Safety and Monitoring Board (DSMB). The DSMB specifies overall monitoring that will be conducted by the principal investigator, including timely reporting of AEs and SAEs. Every 6 months, the DSMB will convene to review the overall safety data, and data on safety summarized by treatment condition. As per NIH guidelines, the objective of these reviews will be to determine whether continued conduct of the trial poses any undue risk for participants.

The DSMB will include 1) a board-certified psychiatrist, Eric Lenze, MD, 2) a cardiologist, Sharon Cresci, MD, 3) an internist specialize in critical care and pulmonary health, Mario Castro, MD, 4) an internist with expertise in stroke prevention and personalized antithrombotic therapy, Brian Gage, MD, and 5) a statistician with expertise in research methodology, especially multicenter clinical trials and analysis of administrative data sets, J. Philip Miller. All five have extensive experience with clinical trials. The DSMB will be blinded through the trial and convene every 6 months to compare the groups with respect to adverse events, dropouts, withdrawals, suicidality, and other problems as well as efficacy. They will make a recommendation at each meeting regarding whether to continue or discontinue the trial, the decision will be adjudicated by the Washington University Human Studies Committee.

4.b Medical Monitoring

The principal investigator will be responsible for routine monitoring of the trial's progress. This monitoring includes scheduled biweekly meetings with study staff and review of written documentation. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number of participants treated and the stage of intervention, a summary and an individual review of any unanticipated health events, and outcome data. In addition, any unanticipated health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the study physicians (PI psychiatrist).

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, follow-up protocols will assess the presence of medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alternations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects. We will refer patients to the study physician as needed.

If participants are smoking regularly, we will tell them to continue taking the study medication and set another quit date as soon as possible. Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

This DSMP requires that investigators notify the Washington University IRB in a timely manner of the occurrence of any unanticipated health events which are severe, unanticipated, and possibly related to study medication or protocol. If the unanticipated health event might be related to the medication use, both the Food and Drug Administration (FDA) and the manufacturer (Glaxo, Inc. or Pfizer, Inc.) will be notified within 5 days of investigators becoming aware of the event. Examples of a serious unanticipated health event would be untoward occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital anomaly/birth defects. Unanticipated health events would include less serious problems that merit reporting because they are severe, unanticipated, and possibly related to study participation. Any serous unanticipated health event will be queried and reported even if it appears that the serious unanticipated health event is unrelated to study participation. The principal investigator will also be responsible for the accurate documentation, investigation, and follow-up of all study-related unanticipated health events.

Unanticipated health event assessment, recording, reporting and investigation will be accomplished through staff training, structure/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The principal investigator has ultimate responsibility for ensuring that unanticipated health events are detected and reported.

4.c Definitions of Adverse Events

Adverse events are assessed in each follow up visit up to the end of treatment.

With respect to the pharmacotherapy, participants will be made aware of the common side effects before they consent to participate in the study. It should be noted that the nicotine patch is available over the counter. The nicotine patch has very few side effects, but participants may have a local skin reaction, and rarely, individuals may have a more systematic allergic reaction. The most common side-effects associated with the nicotine patch are diarrhea, indigestion, nausea and vomiting, dry mouth, muscle and joint pain, sleeplessness, and abnormal dreams. Side effects associated with wearing an adhesive patch include skin rash, redness, and itching or irritation of the skin. In most cases, these side effects have been mild to moderate in intensity and go away once the patch is removed. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible.

4.d Classification of Events

With respect to the pharmacotherapy, participants will be made aware of the common side effects before they consent to participate in the study. It should be noted that the nicotine patch is available over the counter. The nicotine patch has very few side effects, but participants may have a local skin reaction, and rarely, individuals may have a more systematic allergic reaction. The most common side-effects associated with the nicotine patch are diarrhea, indigestion, nausea and vomiting, dry mouth, muscle and joint pain, sleeplessness, and abnormal dreams. Side effects associated with wearing an adhesive patch include skin rash, redness, and itching or irritation of the skin. In most cases, these side effects have been mild to moderate in intensity and go away once the patch is removed. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible.

4.e Data Collection Procedures for Adverse Events

Adverse events are assessed in each follow up visit up to 1 year.

4.f Reporting Procedures

This DSMP requires that investigators notify the Washington University IRB in a timely manner of the occurrence of any unanticipated health events which are severe, unanticipated, and possibly related to study medication or protocol. If the unanticipated health event might be related to the medication use, both the Food and Drug Administration (FDA) and the manufacturer (Glaxo, Inc. or Pfizer, Inc.) will be notified within 5 days of investigators becoming aware of the event. Examples of a serious unanticipated health event would be untoward occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital anomaly/birth defects. Unanticipated health events would include less serious problems that merit reporting because they are severe, unanticipated, and possibly related to study participation. Any serous unanticipated health event will be queried and reported even if it appears that the serious unanticipated health even is unrelated to study participation. The principal investigator will also be responsible for the accurate documentation, investigation, and follow-up of all study-related unanticipated health events.

Unanticipated health event assessment, recording, reporting and investigation will be accomplished through staff training, structure/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The principal investigator has ultimate responsibility for ensuring that unanticipated health events are detected and reported.

4.g Adverse Event Reporting Period

Adverse events will be recorded and reported throughout the entire duration of this study follow up period of 1 year for each participant.

4.h Post-study Adverse Event

Post-study adverse events will be recorded when the subject volunteers to report such events to the investigator team.

E5 Study Outcome Measurements and Ascertainment

Smoking Status and Withdrawal: All subjects will be contacted via phone for assessments of smoking status. We will assess long term outcomes following the SRNT Workgroup recommendations (Hughes et al, 2003).

Primary Outcome Measure:

7-day point prevalence abstinence [Time Frame: Week 12]
The definition of this measure requires: (a) no self-reported smoking (not even a puff of a cigarette) for at least the 7 days prior to the assessment, and (b) CO biochemical verification of abstinence.

Secondary Outcome Measures:

Continuous Abstinence (11 weeks) [Time Frame: 12 weeks with the first 1 week initial grace period]
The definition of this measure requires: Not taking even 1 cigarette puff from target quit date to end of treatment with the first 1 week initial grace period.

7-day point prevalence quit rate [Time Frame: Week 24]
The definition of this measure requires: (a) no self-reported smoking (not even a puff of a cigarette) for at least the 7 days prior to the assessment, and (b) biochemical verification of abstinence.

Number of days to lapse and relapse [Time Frame: Assessed from the target quit day through 52 weeks.]
The number of days to lapse is defined as the number of days from the target quit date until the participant reports smoking (even a single puff). The number of days to relapse is defined as the number of days from the target quit day until the first of seven consecutive days of smoking.

Initial Cessation [Time Frame: Assessed for the first seven days after the target quit date.]
Defined as at least 1 day of abstinence during the first 7 days after the target quit day.

A research assistant will be ascertaining smoking status. Finally, we will gather carbon monoxide (CO) data at 12-wk in-person visits to biochemically validate self-reports: CO>8ppm will indicate smoking.

Other Assessments: WSWS, Environmental factors will be assessed in each follow up visits.

F Statistical Plan

F1 Sample Size Determination and Power

We will recruit 822 subjects for this study to examine whether genotypes predict the efficacy and side effects of cessation medications. The sample size is based on the statistical power calculation based on current research findings. Based on published finding of effect size (OR=3.1), we will have power of 0.84 to detect a hypothesized interaction effect size of 2.0 with the study design (2 sided α=0.05, abstinence rate 20% in the placebo group).

F2 Interim Monitoring and Early Stopping

The principal investigator will be responsible for routine monitoring of the trial's progress. This monitoring includes scheduled biweekly meetings with study staff and review of written documentation. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number of participants treated and the stage of intervention, a summary and an individual review of any unanticipated health events, and outcome data. In addition, any unanticipated health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the study physicians (PI psychiatrist and Safety Consultants cardiologist and internist).

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, follow-up protocols will assess the presence of medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alternations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects. We will refer patients to the study physician as needed. If participants are smoking regularly and heavily (>=5 cigs daily), we will tell them to discontinue taking the study medication.

Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

There is no plan of interim analyses of the primary hypothesis.

F3 Analysis Plan

All analyses will first be conducted separately for European Ancestry (EA) and African American (AA) due to distinctly different allele frequencies and linkage disequilibrium across ancestry. If consistent genetic effects are seen across ancestry, samples of EA and AA ancestry will be combined in analyses with the covariate of race.

We will compare the abstinence outcome in the two placebo groups (placebo nicotine patch plus placebo nicotine lozenge vs. placebo varenicline pill). If they are comparable which is consistent with prior experience of other placebo-controlled smoking cessation trials, they will be pooled for further analyses.

The primary outcome is CO-confirmed point prevalent abstinence at end of treatment (12 weeks), defined if subjects deny smoking during 7 days prior of the end of treatment and provide a breath sample with CO <8 ppm.

Hypothesis #1 is to examine whether medication effect (cNRT vs. placebo) varies with CHRNA5 (i.e. a genotype X medication interaction). A series of generalized linear models will be used to examine main effects of genotype (rs16969968) and medication before testing genotype x medication interactions, with sex, age, and study cohort as covariates using logistic regression models.

Hypothesis #2 is to examine whether medication effect (varenicline vs. placebo) varies with CHRNA5 (i.e. a genotype X medication interaction). A series of generalized regression models will be used to examine main effects of genotype (rs16969968) and medication before testing genotype x medication interactions, with sex, age, and study cohort as covariates using logistic regression models.

Analysis Plan.
We will use generalized linear models with logit as the link function to model the primary outcome (7-day point prevalence abstinence at 12 weeks/end of treatment). We will construct contrast models for each specific hypothesis testing and compare the goodness of fit for each contract. The primary method of analysis will be estimating a standard series of regression equations to test main effects, and gene – environment interaction (effect moderation).

Our primary analyses will focus on SNPs, rs16969968, tagging nicotinic receptor genes *CHRNA5-A3-B4* and medication in our hypotheses testing for gene-medication interactions. Additional covariates include age, gender, measures of nicotine dependence severity (such as pre-quit cigarettes smoked per day), adherence, and non-genetic factors.

Secondary cessation outcomes include CO-confirmed 3-month continuous abstinence with a 1-week grace period, 7-day abstinence at 6 months, and 1 year, time to relapse (using Cox regression models), and withdrawal severity. Generalized Estimation Equation (GEE)[108] will be used in longitudinal models comprising abstinence outcomes across 3 months, 6 months, and 1 year in secondary analyses.

Detailed analysis plan is included in the Statistical Analysis Plan (SAP) in Appendix K10.

F4 Statistical Methods

This is a randomized smoking cessation trial. Simple X^2 tests, logistic regression models and cox proportional hazard models will be used to study the association between genetic markers and cessation outcomes.

We will use generalized linear models with logit as the link function to model the primary outcome (7-day point prevalence abstinence at 12 weeks/end of treatment). We will construct

contrast models for each specific hypothesis testing and compare the goodness of fit for each contract. The primary method of analysis will be estimating a standard series of regression equations to test main effects, and gene – environment interaction (effect moderation).

Detailed analysis plan is included in the Statistical Analysis Plan (SAP) in Appendix K10.

F5 Missing Outcome Data

If a participant prematurely discontinues the study medication, the reason for discontinuation will be determined and classified as primarily due to an adverse event, or lack of efficacy, not wanting to take another medication, or others. We will examine missing data for causes and compare the groups with respect to side effects and efficacy. We will adhere to the intent-to-treat principle for smoking outcome analyses, so that dropouts will be treated as smoking. In addition, we will analyze the missing data under conditions of both missing completely at random (MCAR) and missing at random (MAR), and use appropriate strategies such as imputation when appropriate.

Participants who drop of the trial before they get a dose of the study medication/placebo will be included in the analyses of efficacy if they receive the medication packet. They will be included in the safety analyses if medication was dispensed to them. We will ensure an appropriate informed consent process to minimize the probability of drop out. We will also assess level of adherence to the study protocol and these information will be available for use in secondary analyses.

F6 Unblinding Procedures

The study medication will only be unblinded when there is a moderate to severe adverse event and this information is required for a medical evaluation of the subject. The principal investigator will be notified and make a determination to coordinate study medication unblinding with the participant and the treating physician.

G Data Handling and Record Keeping

G1 Confidentiality and Security

All medical information and data from the interviews will be kept in a locked file cabinet in a locked office and identified by a code number. The master list of subject names will be kept in a separate locked file cabinet in a separate locked office by the Principal Investigator. Computerized research data are identified only by subject identification numbers and codes, and confidential data files are password protected. Written records of counseling sessions will be kept in a locked cabinet and will be destroyed within one year of the termination of the project. Only authorized individuals will be permitted to review these records. We have followed these procedures in the past without any breeches of confidentiality, and we feel certain that we will be able to maintain the same level of security for this project.

We will provide a private setting during the recruitment process in the hospital by the patient's bed and the patient can ask questions privately. The intervention (medication and smoking cessation counseling) will occur in a private setting in the patient's hospital room. We will collect

minimally necessary information from the participant to meet the aims of this study. The follow up phone visits will be made in a private research office.

Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - All medical information and data from the interviews will be kept in a locked file cabinet in a locked office and identified by a code number. The master list of subject names will be kept in a separate locked file cabinet in a separate locked office by the Principal Investigator. Written records of counseling sessions will be kept in a locked cabinet and will be destroyed within one year of the termination of the project. Only authorized individuals will be permitted to review these records. We have followed these procedures in the past without any breeches of confidentiality, and we feel certain that we will be able to maintain the same level of security for this project.

Electronic records (computer files, electronic databases, etc.) - Computerized research data are identified only by subject identification numbers and codes, and confidential data files are password protected.

Questionnaire data and other data that the participants provide will also have a number code (but not the same as the DNA sample) that by itself cannot be linked to the participant. The keys to the codes that link the DNA samples and the other data will be kept at Washington University in a locked cabinet. No analyses or reports will be linked to the participant's name or other information that would allow the participant to be identified.

With respect to genetic data, laboratory staff have no direct contact with GISC participants. Data are stored by ID number. Subject identifiers and personal identifiers are always withheld from the laboratories and, thus, could not be linked to any repository identifiers. Under no circumstances would the laboratories accept any biomaterials or data with any subject identifiers. All identifiers remain with the principal investigator or the designated agents who actually collected blood and data.

G2 Training

All research staff will receive appropriate level of training on HIPPA and patient confidentiality before the study. They will also receive continued education and annual refreshment training on these topics.

Training for smoking cessation counseling is outlined in the smoking cessation counseling guide (Appendix K11). This manual will standardize the counseling and allow the health counselors to follow the guidelines written in this smoking cessation counseling guide.

G3 Case Report Forms and Source Documents

Data that the participants provide will also have a number code (but not the same as the DNA sample) that by itself cannot be linked to the participant. The keys to the codes that link the DNA samples and the other data will be kept at Washington University in a locked cabinet. No analyses or reports will be linked to the participant's name or other information that would allow the participant to be identified.

G4 Records Retention

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G5 Performance Monitoring

The principal investigator will be responsible for routine monitoring of the trial's progress. This monitoring includes scheduled biweekly meetings with study staff and review of written documentation. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number of participants treated and the stage of intervention, a summary and an individual review of any unanticipated health events, and outcome data. In addition, any unanticipated health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the study physicians (PI psychiatrist and Safety Consultants cardiologist and internist).

H Study Monitoring, Auditing, and Inspecting

H1 Study Data Safety and Monitoring Plan

This study has a Data Safety and Monitoring Plan (DSMP), and a Data and Safety Monitoring Board (DSMB). The Individual Patient Safety Committee (IPSC) will include three of the study's key personnel: Li-Shiun Chen, M.D., M.P.H., Sc.D., a psychiatrist; Robert Carney, Ph.D., a psychologist, Laura Bierut, M.D., a psychiatrist; The IPSC will review monthly reports on all participants. The IPSC will be blinded to the patient's group assignment.

The principal investigator will be responsible for routine monitoring of the trial's progress. This monitoring includes scheduled biweekly meetings with study staff and review of written documentation. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number of participants treated and the stage of intervention, a summary and an individual review of any unanticipated health events, and outcome data. In addition, any unanticipated health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the study physicians (PI psychiatrist and Safety Consultants cardiologist and internist).

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, follow-up protocols will assess the presence of medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alternations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects. We will refer patients to the study physician as needed. If participants are smoking regularly, we will tell them to continue taking the study medication and set another quit date as soon as possible. Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will

be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

This DSMP requires that investigators notify the Washington University IRB in a timely manner of the occurrence of any unanticipated health events which are severe, unanticipated, and possibly related to study medication or protocol. If the unanticipated health event might be related to the medication use, both the Food and Drug Administration (FDA) and the manufacturer (Glaxo, Inc. or Pfizer. Inc.) will be notified within 5 days of investigators becoming aware of the event. Examples of a serious unanticipated health event would be untoward occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital anomaly/birth defects. Unanticipated health events would include less serious problems that merit reporting because they are severe, unanticipated, and possibly related to study participation. Any serous unanticipated health event will be queried and reported even if it appears that the serious unanticipated health even is unrelated to study participation. The principal investigator will also be responsible for the accurate documentation, investigation, and follow-up of all study-related unanticipated health events.

Unanticipated health event assessment, recording, reporting and investigation will be accomplished through staff training, structure/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The principal investigator has ultimate responsibility for ensuring that unanticipated health events are detected and reported.

In addition, we have a Data Safety and Monitoring Board (DSMB). The DSMB specifies overall monitoring that will be conducted by the principal investigator, including timely reporting of AEs and SAEs. Every 6 months, the DSMB will convene to review the overall safety data, and data on safety summarized by treatment condition. As per NIH guidelines, the objective of these reviews will be to determine whether continued conduct of the trial poses any undue risk for participants.

The DSMB will include 1) a board-certified psychiatrist, Eric Lenze, MD, 2) a cardiologist, Sharon Cresci, MD, 3) an internist specialize in critical care and pulmonary health, Mario Castro, MD, and 4) an internist with expertise in stroke prevention and personalized antithrombotic therapy, Brian Gage, MD, and 5) a statistician with expertise in research methodology, especially multicenter clinical trials and analysis of administrative data sets, J. Philip Miller. All five have extensive experience with clinical trials. The DSMB will be blinded through the trial and convene every 6 months to compare the groups with respect to adverse events, dropouts, withdrawals, suicidality, and other problems as well as efficacy. They will make a recommendation at each meeting regarding whether to continue or discontinue the trial, the decision will be adjudicated by the Washington University Human Studies Committee.

H2 Counseling Monitoring Plan

Patients will be seen by the health counselor at the baseline visit and the health counselor will provide smoking cessation counseling as outlined in the smoking cessation counseling guide. Following visit 1, follow-up phone calls will be made at the last day of pre-quit, quit date, 1, 2, 4, and 12 weeks post quit date to provide counseling sessions. The last counseling session at 12 weeks post quit date may be in person or over the phone. The monitoring plan is outlined in the smoking cessation counseling guide.

H3 Auditing and Inspecting

The Individual Patient Safety Committee (IPSC) will include two of the study's key personnel: Li-Shiun Chen, M.D., M.P.H., Sc.D., a psychiatrist; Robert Carney, Ph.D., a psychologist; Laura Bierut, M.D., a psychiatrist; . The IPSC will review monthly reports on all participants. The IPSC will be blinded to the patient's group assignment.

I Study Administration

I1 Organization and Participating Centers

Barnes Jewish Hospital at Washington University is the only site for this study.

I2 Funding Source and Conflicts of Interest

The NIH career development award of Dr. Li-Shiun Chen will fund this study.
The NIH R01 of Dr. Li-Shiun Chen which received a just in time request in 6/2014 will fund this study.

I3 Committees

The Individual Patient Safety Committee (IPSC) will include two of the study's key personnel: Li-Shiun Chen, M.D., M.P.H., Sc.D., Robert Carney, Ph.D., a psychologist; a psychiatrist; Laura Bierut, M.D., a psychiatrist; . The IPSC will review monthly reports on all participants. The IPSC will be blinded to the patient's group assignment.

We have a Data Safety and Monitoring Board (DSMB) which will convene to review the overall safety data, and data on safety summarized by treatment condition every 6 months. The DSMB will include 1) a board-certified psychiatrist, Eric Lenze, MD, 2) a cardiologist, Sharon Cresci, MD, 3) an internist specialize in critical care and pulmonary health, Mario Castro, MD, and 4) an internist with expertise in stroke prevention and personalized antithrombotic therapy, Brian Gage, MD, and 5) a statistician with expertise in research methodology, especially multicenter clinical trials and analysis of administrative data sets, J. Philip Miller. All five have extensive experience with clinical trials. The DSMB will be blinded through the trial. They will make a recommendation at each meeting regarding whether to continue or discontinue the trial, the decision will be adjudicated by the Washington University Human Studies Committee.

I4 Subject Stipends or Payments

We will compensate subjects with a cash of $25 for the initial visit (if blood sample is needed), $25 for Visit one if initial visit was needed, $40 for Visit 1 if initial visit was not needed, $20 for completing phone calls at Visit 7 (12 weeks post-quit) and $20 for Visit 8 (6 months post-quit), and $10 when they complete phone Visit 9 (1 year post-quit). If participants are asked to come in to verify abstinence, we will compensate subjects with an additional $20 per in person visit. The total compensation is up to $140 if they complete the study.

I5 Study Timetable

The recruitment of 822 participants will take place in the first 3 years of this study and the 1 year follow up of the last participant will be completed in the end of the fourth year.

J Publication Plan

We plan to publish the results in international conference and addiction related journals.

K Attachments

K1 Informed consent

K2 Baseline Interview

K3 Follow up Interview

K4 Beck Depression Inventory

K5 Beck Anxiety Inventory

K6 Initial Contact Letter

K7 Screening Log

K8 Contact Form

K9 Patch Use Instruction/Pill Use Instruction

K10 Detailed statistical analysis plan (SAP)

K11 Smoking Cessation Counseling Guide

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