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Translational Neuropsychopharmacology Research of Nicotine Addiction
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Medical University of South Carolina
Protocol

Translational Neuropsychopharmacology Research of Nicotine Addiction

Principal Investigator(s):
Brett Froeliger, Ph.D.,
Kevin Gray, M.D.

Co-I:
Erin McClure, Ph.D.

A. Summary of Protocol

a. Brief Description of Protocol (Study Design)

This study will examine the effects of combining Varenicline (VRN) and *N*-acetylcysteine (NAC) on neural circuitry function and treating nicotine addiction. Healthy adult nicotine dependent cigarette smokers interested in quitting (n=150) will be randomized to one of four PBO-controlled conditions for 4 weeks: 1) VRN+NAC, 2) VRN+PBO, 3) NAC+PBO or 4) PBO+PBO. Following 1 week of medication, participants will be contingently reinforced for 3 days of smoking abstinence and be scanned using functional magnetic resonance imaging (fMRI) techniques, while nicotine deprived during a resting state and a cue-reactivity (CR) task. Participants will be followed over the next 3 weeks of treatment and clinical variables will be assessed.

b. Specific Aims

Aim 1. Identify the effects of *N*-acetylcysteine (NAC) + Varenicline (VRN) on resting neural network function and behavior. We will examine the individual and combined effects of VRN and NAC on neural circuitry function in humans. We will also identify relations between neural circuitry function and nicotine/smoking self-administration, withdrawal symptom severity and the maintenance of smoking abstinence over the duration of the study.

Aim 2. Examine the effects of NAC+VRN on drug-cue brain response and behavior. We will examine the individual and combined effects of VRN and NAC on cue-induced brain response and behavior in humans, focusing on limbic-striatal and corticostriatal networks. In these experiments we will also identify relations between neural circuitry function and nicotine/smoking self-administration and withdrawal symptom severity and the maintenance of smoking abstinence over the duration of the study.

Exploratory Aim: Participants will complete a Smoking Regulation Relapse task (SRRT) in the laboratory—the effects of VRN+NAC on smoking topography during the SRRT, and on subsequent smoking behavior and relapse will be examined. Whole brain fMRI analyses will be conducted, and relations between fMRI measures and clinical outcomes will be examined.

B. BACKGROUND AND SIGNIFICANCE

Cigarette (henceforth nicotine) addiction is a chronic, relapsing brain disorder and remains the leading preventable cause of death and disability in the US [1], costing nearly $200 billion each year [2]. Although ~20% of adults in the USA currently smoke [3], the majority want to quit. In spite of the breadth of research focused on improving health outcomes and reducing the societal burden caused by nicotine addiction, the majority of smokers who attempt to quit will relapse. Nicotine withdrawal-related disturbances in executive function, negative affect and reward processes compel a smoker to self-administer nicotine—each in turn representing the loss of control to remain abstinent and risk factors for relapse [4]. Thus, identifying the effects of nicotine addiction on mechanisms of self-regulation, and the value of novel medications for remediating dysregulated behavior are both needed in order to enhance interventions for treating nicotine addiction. Our preliminary data, along with the extant literature, suggest that the maintenance of nicotine addiction is subserved by dysregulated neural function in limbic-striatal and corticostriatal neural circuitry. While VRN may be effective in treating limbic-striatal circuitry that is associated with promoting abstinence and reducing acute withdrawal; NAC may be effective in treating corticostriatal circuitry function that is associated with relapse vulnerability. Thus, the current proposal seeks to investigate two medications (VRN & NAC), with potentially complementary effects on the two different brain circuits— limbic-striatal (VRN) and corticostriatal (NAC) circuitry—and that may therapeutically target two different phases in the recovery of nicotine addiction—the promotion of abstinence (VRN) and relapse prevention (NAC). The placebo (PBO)-controlled design in this proposal will allow the team to identify and translate between the neurobiological substrates and the neurocognitive underpinnings of the effects of VRN+NAC on smoking behavior in humans—thus, advancing our understanding of the pathophysiology of nicotine addiction.

C. RESEARCH DESIGN AND METHODS

Protocol Overview (see Fig. 1). Adult smokers interested in quitting smoking (n=1502) will be randomized to one of four PBO-controlled conditions for four weeks: 1) NAC+VRN, 2) NAC+PBO, 3) VRN+PBO, or 4) PBO+PBO. Following one week of treatment, participants will be contingently reinforced for three days of smoking abstinence and be fMRI scanned.

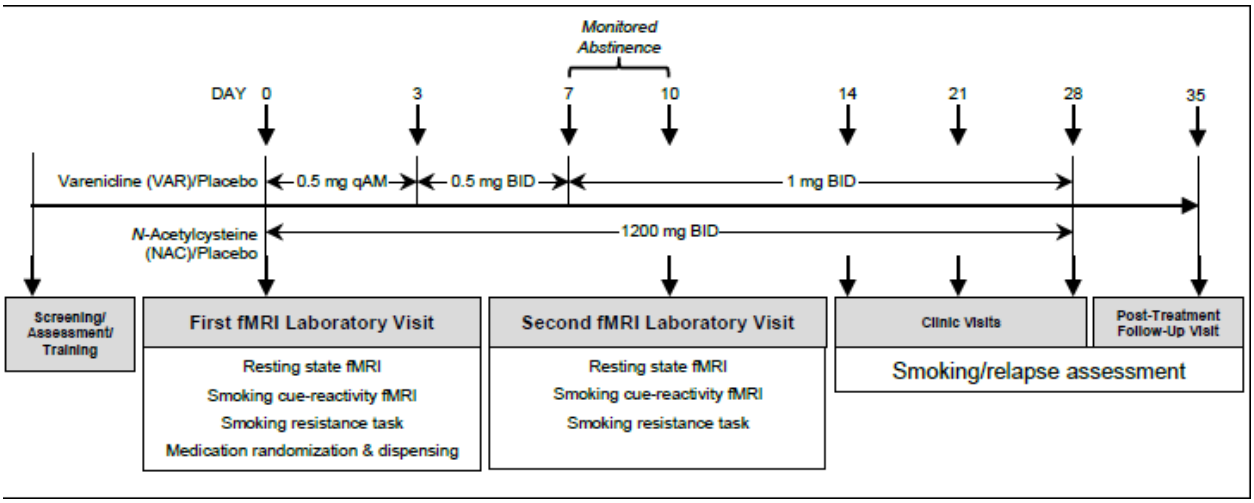

Figure 1. Protocol for human research. Following 3-days of smoking abstinence, participants will undergo fMRI during a resting state (Aim 1a) and smoking CR task (Aim 2a). At the end of the visit, participants perform the SRRT- a laboratory smoking relapse analog task to characterize the effects of medication on craving regulation and smoking-self administration (exploratory aim). Participants will be followed over the next 3-weeks of treatment and relations between smoking outcomes (e.g. time to lapse), withdrawal symptoms (e.g. craving, mood) and fMRI measures will be examined (exploratory aim).

Immediately following scanning, participants will undergo the Smoking Regulation Relapse Analog Task (SRRT) and smoking topography measures (e.g. time to first puff, number of puffs) will be recorded. Participants will be followed over the next three weeks of treatment and clinically relevant behaviors will be assessed. The effects of treatment conditions between fMRI measures, the SSRT, and smoking behavior over the subsequent three weeks will be examined.

Participant recruitment and selection. We plan to enroll 150 adult smokers (ages 18-65) who are interested in or contemplating quitting smoking in order to obtain 100 complete datasets. We will recruit participants from the Charleston metropolitan area in which MUSC is located. Participants will be recruited through the TRAIN Laboratory Database Repository (PI: Froeliger, PR: 23098), additional databases of participants that have agreed to be contacted for future studies (PI: Gray, consent provided within study-specific consent forms), IRB-approved advertisements in regional newspaper, flyers, ResearchMatch, and on internet sites affiliated with our laboratory and the medical center. These advertisements will briefly describe the study and ask interested individuals to contact the study coordinator. Individuals interested in participating will undergo a phone screen to determine eligibility and those who meet study criteria will be invited to our offices for a detailed screening visit.

The study will incorporate a Community Recruitment Vendor (CRV) campaign to assist in reaching out to the targeted study population. By identifying persons/businesses in the local area we will establish an agreement whereby for a monthly retainer, the CRV will promote the study using IRB approved recruitment materials within their unique network. The CRV will also be able to receive a bonus if a prospective participant identifies the CRV as their referral source and is successfully enrolled into the study protocol.

At the screening visit, informed consent, self-reported mood, smoking history, medical history, MINI International Neuropsychiatric Interview (MINI), and an MRI safety screening questionnaire will be administered by trained study staff and reviewed by approved study clinicians. Participants meeting all selection criteria will be scheduled for subsequent sessions

As with previous studies, we will make every effort to maximize participant retention via a thorough informed consent process, careful screening, and other practices (e.g., contacting participants with a reminder phone call the night before experimental sessions). A complete list of questionnaires and cognitive tasks that will be completed at each visit are included in Appendix 1.

The PI and research staff have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. Male and female adult smokers, between 18 and 65years old, will be recruited, primarily through media advertisements (i.e. internet, print, radio). The inclusion/exclusion criteria are as follows:

Entry Criteria

Inclusion Criteria all subjects:

1. Age 18 - 65
2. English fluency as demonstrated in providing informed consent and the ability to independently follow directions in completing assigned assessments and tasks
3. Functional vision (with corrective lenses as needed) to complete assigned assessments and tasks
4. Current nicotine dependent cigarette smoker with a minimum smoking history of two years
5. Interest in quitting smoking or contemplating a quit attempt in the next 6 months
6. If female, agreement to use birth control (any form of hormonal contraception such as Depo-Provera, daily oral contraception, transdermal patch, or Nuva-ring; intrauterine device; sterilization; or double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm) to avoid pregnancy
7. Refrain from all other tobacco (i.e. dip/chew, cigars, cigarillos) and/or nicotine products (i.e. e-cigs, patches, gum/lozenges, inhalers/sprays) for the duration of study participation

Exclusion Criteria all subjects:

1. Past head injury or primary neurological disorder associated with MRI abnormalities, including dementia, MCI, brain tumors, epilepsy, Parkinson's disease, or demyelinating diseases
2. Any physical or intellectual disability affecting completion of assessments
3. Any contraindication to MRI
4. Positive urine drug screen for illicit substances (other than marijuana or cocaine). 4a. For those testing positive for marijuana and/or cocaine, meet dependence criteria
5. Current or past psychosis
6. Electroconvulsive therapy in last 6 months
7. Use of antidepressants, medications with smoking cessation efficacy, or other psychotropic medications in the last month.
8. Positive urine pregnancy test or current breast-feeding status
9. Any other condition or concern that in the Investigator's opinion would impact participant safety, compliance with study instructions, or potentially confound the interpretation of the study results

As part of exclusion criteria #9, participants are specifically asked to not take part in any other research during their active participation in the protocol once eligibility at screening is made through the last visit day of the protocol.

Among females, pregnancy at screening will be exclusionary. Females of childbearing potential must agree to undergo additional pregnancy testing on Days 0 and 10 prior to the fMRI

scanning sessions and before randomization into the medication portion of trial. They must further agree to notify the study physician or PA if they become pregnant during the study. *Screening/Training Visit (Day -0).* During screening, all aspects of the study will be described to subjects and informed consent will be acquired. A breath sample will be collected in order to verify smoking status. Blood, expired carbon monoxide (CO) and urine samples will be obtained in order to assess baseline nicotine and cotinine values, pregnancy status for females, and to screen for illicit drug use. For female participants, the urine pregnancy screen will be performed prior to a drug screen and only if it is negative will the drug test be conducted. If the pregnancy screen is positive, the participant will be excluded from the study and no further study procedures will be performed. Participants will then undergo a physical evaluation by the study Physician (PI: Gray) or PA-C as delegated, and a blood sample collected at the Clinical Neurobiology Lab (CNL) located at 67 President St. Participants will also provide a breath sample to screen for intoxication (ALERT J5 Alcohol Tester, ACS Corporation). If participants' blood-alcohol content (BAC) is higher than 0.0, they will be rescheduled for the following week. If a participant tests positive for alcohol more than once during the course of the study, he/she will be discontinued. Next, participants will fill out paper demographic forms, medical and employment histories, and an MRI safety checklist. Participants will then fill out a battery of questionnaires to assess baseline smoking behavior, mood, and cognitive function. Following the questionnaires, trained study staff will administer the MINI International Neuropsychiatric Interview (MINI) to assess for substance use disorders (SUDs) and major psychiatric illnesses. If participants continue to be eligible following the application of the screening criteria, they will continue onto the training portion of the visit where they will become familiarized with the fMRI environment. Here they will practice tasks while inside a mock scanner in order to reduce scan-related anxiety and improve data quality.

Genetic Evaluation Procedure. After the subject gives informed consent, we will collect a venous blood sample of 15 ml. Blood samples obtained from this study will be collected at CNL and stored in the Translation Research on Addiction and Integrative Neuroscience (TRAIN) Laboratory directed by Dr. Froeliger. The blood samples will be analyzed at CNL and will be coded so that researchers analyzing DNA will have no way of identifying participants. We will use the DNA to examine if there are any relationships between brain functioning and genetic factors. There will be no identifiers except for a code number on the samples. A digital key to the code numbers will be maintained in password protected database on the MUSC network. The study PI (Dr. Froeliger) will have access to the password.

Randomization & fMRI Session 1 (Day 0). During this session, participants will provide breath and urine samples to characterize current smoking behavior and BAC and fill out questionnaires to assess mood, cognitive state, and to characterize recent alcohol and nicotine use. Prior to receiving their study medication, both the participant and the research staff completing the visit will complete the Penetration of the blind (POB) assessment. POB completion by the participant and staff is done separately outside the presence of one another. At future visits when the POB is completed, research staff will complete their assessment at the conclusion of the visit without having viewed the participant's response.

Next, participants will be educated on guidelines for taking study medication and will be randomly assigned to one of four double-blind study medication arms: 1) NAC+VRN, 2) NAC+PBO, 3) VRN+PBO, or 4) PBO+PBO. Adverse events will be monitored throughout the study participation at every subsequent visit and participants will be encouraged to contact the study team in the interim if issues/concerns surrounding their medication and/or change in baseline health were to occur.

Participants will also be given instruction on their daily diary which logs the participant's smoking and related behaviors, as well as receive brief counseling on cessation strategies. They will also be given a take home resource material that may be helpful with their quit attempt.

While in the MRI scanner for their baseline session, fMRI-1, participants will lie still while undergoing a high resolution anatomical scan, as well as perform the CR task. Participants will be inside of the MRI scanner for approximately one hour. After the scanning portion of the visit, participants will perform the SRRT and smoke a cigarette through the CReSS smoking topography system.

Cue Reactivity Task (CRT). Participants will be scanned while performing a smoking CR task that involves viewing cigarette smoking-related images (e.g. cigarette) and non-smoking control images (e.g. pencil) over the course of ~8 ½ minutes [5, 7-13]. Participants will be asked to periodically report their level of craving in response to the images.

Smoking Regulation Relapse analog task (SRRT: Fig. 2. The SRRT was developed by the PI (Froeliger), and currently in use in his laboratory to assess relations between success in regulating mood and craving and subsequent smoking self-administration. The task is comprised of two phases. The first phase—similar to [6]— presents smoking or neutral images and instructs participants to either react to how the stimulus would make you feel Now (e.g. immediate satisfaction) or reframe the content into how it would make you feel Later (e.g. the deleterious health effects of smoking). Following each trial, self-reported craving ratings are collected. This is shown to be an effective probe of craving regulation that is mediated by corticostriatal function [6]. The task randomly presents 24 trials of neutral (n=12) and smoking (n=12) images, half of each divided into instruction with Now or Later, over a 6-min block. Participants have the choice to earn $1 for each subsequent block up to 60 min., or quit the task and smoke a cigarette using a pocket CReSS system and topography measures recorded (e.g. # puffs, puff volume, IPI). In order to verify smoking topography measures, participants will be video recorded during while smoking through the CReSS device. Preliminary findings from a mood-regulation variant of the SRRT developed by

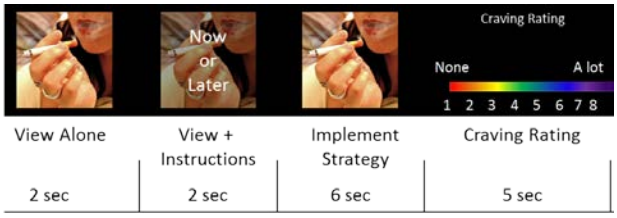

Figure 2: SRRT. Participants view control and smoking-related images and instructed to either react (Now) or regulate (Later) their response to the image and then rate their level of craving. Following the task, participants smoke their preferred brand of cigarettes using the CReSS system. Relations between self-report craving on the SRRT and smoking topography (e.g. # puffs, puff volume) will be examined.

the PI that is currently being used in a NIDA-funded study reveal that the magnitude of adaptive response in dACC during regulation is associated with less smoking self-administration ($r^2 = .52$, $p<.05$). Furthermore, NAC's strengthening of rsFC between the nucleus accumbens and dACC, as shown in Fig. 4, is associated with less smoking self-administration during the SRRT.

Study Medication and Randomization. This is a double-blind, placebo-controlled study of NAC and VRN. Participants will be randomly assigned to one of four double-blind experimental arms: 1) NAC+VRN, 2) NAC+PBO, 3) VRN+PBO, or 4) PBO+PBO. Participants will be instructed to begin tasking study medication the morning of Day 1. Medication response and tolerability/AEs will be assessed by study research staff, and revised by the clinical team as needed

- N-Acetylcysteine (NAC). NAC (or identical-appearing PBO) will be dosed at 1200 mg twice daily throughout the 28-day active treatment. The most common adverse effects of oral NAC are gastrointestinal discomfort (e.g. diarrhea, flatulence, nausea), but this medication is generally well-tolerated [18].
- Varenicline (VRN). VRN (or identical-appearing PBO) will be provided at the standard recommended dose (0.5 mg daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily thereafter for the remainder of active treatment). The most common adverse effects of VRN are nausea, vivid dreams, and insomnia.
- Medication Compounding, Packaging, Dispensing, and Adherence Monitoring. The MUSC Investigational Drug Service (IDS) will be responsible for medication randomization, compounding, packaging, and dispensing. Pill counts and participant daily diaries will be used as additional medication adherence measures.

Abstinence Period (Days 7-10). Smoking abstinence from the target quit date (Day 7) until Day 10 will be confirmed via breath CO samples (abstinence <6 ppm). Participant diaries and medication packs will be reviewed for safety and compliance. Brief assessments on craving, mood and withdrawal symptoms will also be completed.

fMRI -2 Experimental Visit (Day 10). Participants will be contacted two days prior to the schedule fMRI session and reminded of session-specific details. Participants will fill out questionnaires regarding mood, withdrawal symptoms, and caffeine, nicotine, and food intake over the last 24 hours. Expired CO and BAC will be collected to confirm compliance. While in the MRI scanner, participants will lie still while undergoing a high resolution anatomical scan, as well as perform the CR task. Participants will be inside of the MRI scanner for approximately one hour. After the scanning portion of the visit, the participant will complete the POB assessment followed by the participant performing the SRRT and smoking a cigarette through the CReSS smoking topography system. Participants will again be video recorded while smoking through the CReSS device for visual confirmation of the device data collection.

Follow-Up Assessments (Days 11-35). After the fMRI session, participants will continue to take study medication for another 18 days (Days 11-28). They will return to the clinic on Days 14, 21, 28, and 35 to submit expired CO and urine samples to determine smoking status and medication compliance, as well as complete mood, nicotine craving/withdrawal, and safety assessments. Participants will return to the clinic on Day 35 for a one-week post medication safety, smoking assessment, and POB.

At the discretion of the PI's additional urine drug screens, pregnancy, and cotinine tests can be added to a visit day in order to address any unexpected safety and or data integrity concerns within a participant's active participation within the protocol. As needed when urine cotinine collection is not feasible, saliva specimens will be collected for cotinine assay.

Duration. Participation in the study will take about 6 weeks with a total of 10 visits lasting approximately 13-14 hours in total. The first visit (screening/training) will last up to 4 hours; each of the 7 clinic visits (Days 7-9,14-35)) will last about 15 minutes each, and the fMRI Experimental visits (Day 0 and 10) will each last approximately 4 hrs.

Participant Compensation. Participants will be compensated up to $500 for completion of all study procedures. Participants will receive $60 for the screening visit ($20 for successful completion of the blood draw, online surveys, and MINI Plus clinical interview, and $40 for completing the training portion of the visit), $110 for the baseline fMRI-1 (Day 0) and experimental fMRI-2 sessions (which includes $1 for every 6 minutes during SRRT up to 60 minutes total), $60 for achieving biochemically-confirmed abstinence from smoking for 3 days ($20/day), $30 for each additional clinic visit (Days 14-35) to assess smoking status and complete assessments, and an additional $40 bonus for completing all study procedures. Compensation will be made for each session completed and will not be contingent upon completion of the entire study. During the informed consent procedure, participants will be notified that they can withdraw from the study at any time under no penalty.

Additionally, due to the structured nature of the protocol's visit schedule, when a participant is unable to meet a scheduled visit (Days 7-10) due to an unforeseen conflict (i.e. transportation issue), study personnel will explore alternatives (i.e. provide for taxi service) to allow for the visit schedule to continue as planned.

Data Analysis.

<u>fMRI data preprocessing.</u> fMRI data will be preprocessed using SPM8 to remove noise and artifacts, correct for slice acquisition time, motion corrected [14], temporally realigned using B-spline interpolation, normalized into standard stereotaxic space (MNI) with an isotropic 2mm voxel size and smoothed with an 8mm FWHM Gaussian filter. <u>Voxel-wise, within-mask analysis.</u> At the 1st-level, data will be analyzed using the GLM [15]. Each of 2 blocks of interest (Drug, Control) will be modeled as a boxcar canonically convolved hemodynamic response function, and in scanner heart-rate, respiration rate and motion parameters will be entered as nuisance covariates. Next, Drug-Control contrast images will be generated, entered into a 2nd-level, 2 (VRN: Yes, No) x 2 (NAC: Yes,

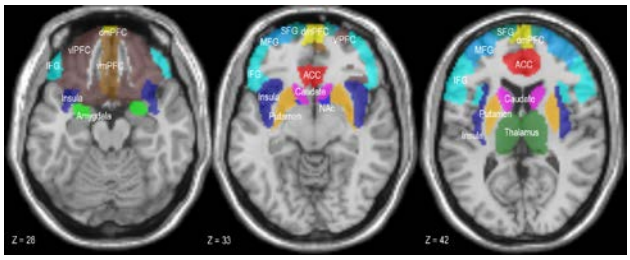

Figure 3. ROI: superior, middle, & inferior frontal gyri (SFG, MFG, IFG), dorso- & ventro-medial, ventrolateral and prefrontal cortex (dmPFC, vlPFC, vmPFC), anterior cingulate cortex (ACC), insula, amygdala, putamen, nucleus accumbens (NA), caudate & thalamus.

No) ANOVA, and analyzed within an ROI mask (Fig. 3), $p < .05$, corrected for multiple comparisons. fMRI data analysis plan: Resting-state functional connectivity will be assessed using the conn13 SPM8 toolbox. First, experimental design variables, pre-processed functional images filtered with a 0.01 to 0.08 Hz band-pass filter and normalized (modulated to preserve volume) T1 and segmented images will be uploaded into the toolbox. 5-mm spheres will be created around MNI coordinates for *a priori* regions of interest (ROIs) that include: bilateral amygdala, nucleus accumbens, dACC and inferior, middle and superior frontal gyri. The conn13 toolbox uses PCA to isolate potentially confounding noise from nuisance covariates using default settings. Individuals' WM and CSF templates, in-scanner heart-rate (HR), respiration rate and movement parameters will be included as covariates. Connectivity matrix for the nucleus accumbens and amygdala seeds will each be entered into separate: 2 (NAC: Yes, No) x 2 (VRN: Yes, No) ANOVAs. We will follow-up with exploratory whole brain analyses.

Brain-behavior data analysis plan: First, POMS, SJW and mCEQ subscale scores will be computed, and motivation to smoke and days to first cigarette (lapse) following the experimental visit will be recorded for each subject. Next, to examine the interactive effects of treatment on self-report and rsFC, each scale will be entered as a regressor of interest in separate between subjects ANOVA's in the Conn Toolbox.

Smoking topography analysis plan. Craving regulation performance will be assessed by calculating change scores (Later-Now) from craving ratings. T-tests will be performed to analyze correlations between craving ratings, smoking topography variables: time to 1st puff (i.e. task blocks); puff volume (milliliters) and number of puffs. Regression analyses will explore relations between SSRT performance and strength of rsFC between ROI's in Figure 11.

Real-world smoking behavior analysis. Number of days to lapse (DTL) following the lab visit on day 10 will be recorded. Regression analyses entering DTL on brain cue-reactivity and rsFC will be performed and relations explored.

D. PROTECTION OF HUMAN SUBJECTS

Risk/Benefit Assessment

The main study procedures include a medication trial, clinical evaluation, MRI, blood draw (with a volume to be collected < 50mL), and completion of questionnaires. The primary risks of the study are a) adverse effects of study medications, b) emotional distress, c) incidental findings, and d) loss of confidentiality.

1. Interview and psychiatric emergencies. Subjects may experience discomfort during the clinical interview and evaluations when discussing symptoms, life events, and social support. The Research Coordinator and Specialists will be experienced and skilled in interviewing subjects. Should the subject wish to stop or take a break, they will allow it. In addition, should the subject express any physical or psychological symptoms that are concerning or possibly represent an emergency, the study physician (Dr. Gray) or other approved study clinician will be contacted immediately to assess the subject and to

determine the appropriate course of action. Possible situations where this would occur include but are not limited to thoughts of suicide, homicidal or violent thoughts, psychosis, or a change in the subject's physical status if they start feeling bad or complaining of new physical symptoms (such as chest pain, acute nausea, etc.). Importantly, the Research Coordinator/Specialist is not the only individual screening for such potential emergencies. These domains will be independently assessed by Dr. Gray/PA-C during the health and physical exam and any subsequent future clinical interview. Options for addressing such emergencies may include contacting the individual's mental health caregiver, referring for urgent evaluation and treatment, or emergent hospitalization.

2. Study Medication. The varenicline package insert details adverse events associated with the medication. Specifically, it reports that "the most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting." Meta-analyses of the four main adverse events in varenicline versus placebo groups in adult trials yielded relative risks (RRs) of 3.21 (95% CI 2.71, 3.80) for nausea, 1.50 (95% CI 1.26, 1.79) for insomnia, 2.79 (95% CI 2.09, 3.72) for abnormal dreams, and 1.20 (95% CI 1.00, 1.45) for headache [16]. While post-marketing anecdotal reports of psychiatric adverse events led to an FDA "black box" warning for varenicline, a reanalysis of controlled trials revealed no evidence that varenicline is associated with neuropsychiatric adverse events [17].

   N-acetylcysteine (NAC) has a long-established safety record in adults and children, with FDA approval since 1963. A meta-analysis of studies evaluating long-term oral treatment with NAC for prevention of chronic bronchitis found that NAC was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption [18].

   The informed consent process will be used to thoroughly educate participants about potential medication-related risks. Rigorous screening procedures and strict exclusion criteria are designed to exclude potential participants at elevated risk for adverse events. This includes comprehensive medical and psychiatric assessment and evaluation. The study physician (board certified psychiatrist), or the physician assistant under his direct supervision, will conduct serial medication management sessions weekly throughout treatment, providing comprehensive, detailed adverse event monitoring. Participants will have access to the study medical clinician 24 hours, 7 days a week for emergencies. Participants experiencing intolerable adverse events will have the opportunity to reduce dose or discontinue medication altogether, while remaining in the study for ongoing monitoring. The study physician has full admitting privileges at the Medical University of South Carolina, in the event that symptom acuity warrants intensive intervention. Urine pregnancy tests will be conducted serially throughout treatment for female participants.

3. Magnetic Resonance Imaging. Although this procedure is generally low-risk, there are particular concerns. Individuals will be screened for the presence of implanted metal (including but not limited to medical devices, shrapnel, tattoos or permanent makeup); those

who screen positive will be excluded from the study. Some participants may feel uncomfortable or confined once positioned within the bore of the MRI system. This potential reaction is reduced by discussing the procedure prior to entry into the magnet room and by communicating with the subject regularly over the intercom. Most importantly, participants will be exposed to the scanning environment through the use of both a mock scanner and a scanner simulator. During the MRI, subjects will have voice contact with a radiology technician, and may request the scan be stopped at any time. If a participant feels uncomfortable in the scanner, the imaging procedure is terminated and the participant is removed from the magnet.

4. Incidental Findings: Magnetic Resonance Imaging: Another risk is the occurrence of incidental findings on MRI, such as risk of previously unrecognized stroke, hematomas, or other findings. All scans are reviewed at time of acquisition. Should any concerning findings be seen, we will obtain a consultation from a clinical neuroradiologist who will provide an opinion on the significance of the finding and recommendations for further evaluation. Dr. Froeliger will contact the subject in question, convey these findings and recommendations, and facilitate referrals for further evaluation and treatment as needed.

5. Incidental Findings: Medical Evaluations: It is possible that subjects will present with vital sign irregularities needing further evaluation. With the subject's permission, such results will be shared with each subject's treating physician. For urgent findings, such as substantially elevated blood pressure, study staff will contact Dr. Gray or another approved study clinician, who will evaluate the subject as needed and make recommendations for what further assessment is needed. Possible options include referral to the subject's treating provider or other urgent or emergent evaluation.

6. Phlebotomy: Subjects will have blood drawn by experienced phlebotomists in the TRAIN Laboratory. Every effort is made to minimize risks, which include hematoma, infection, fainting, and excess blood loss. Sterile technique is used to minimize infection risk, and subjects are asked to apply a pressure with a gauze pad to prevent excess bleeding.

7. Breach of confidentiality: There is the potential risk of breach of confidentiality of clinical and laboratory information. Dr. Froeliger has experience as an investigator dealing with such sensitive information and has experience assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file. Participants' initials will also be present on some questionnaires; however, the questionnaires containing the initials will be stored in a locked file cabinet. Video clips will be stored on a password protected server and viewed by only approved research staff.

Similar safeguards are followed for storage and processing of MRI data. MRI data is stored on secure storage owned by the Center for Biomedical Imaging (CBI). CBI has a longstanding policy of reviewing all scans that are transferred to the laboratory from the MRI scanners, and

assuring that all subject identifiers are removed, both from the scan image itself but also the electronic headers of the scan. The MRI scans are identified only by subject code, study code, and date of acquisition.

Potential Benefits

Participants in the study, regardless of randomization group, will benefit by receiving a) comprehensive medical and psychiatric evaluation, and b) weekly smoking cessation medication management visits with the study medical clinician throughout active treatment.

Importance of the Knowledge to be Gained

The overall benefit is an increase in our understanding of the neurobiological mechanisms underlying nicotine addiction and the novel combination of NAC+VRN for treating nicotine addiction. This will help us better understand the pathophysiology of smoking and provide valuable information guiding subsequent clinical trials.

Targeted Enrollment Table

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	5	5	10
Not Hispanic or Latino	70	70	140
Ethnic Category: Total of All Subjects *	75	75	150
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	25	25	50
White	48	48	96
Racial Categories: Total of All Subjects *	75	75	150

DETAILED DATA SAFETY AND MONITORING PLAN

Translational Neuropsychopharmacology Research of Nicotine Addiction

Kevin M. Gray, M.D., and Brett Froeliger, Ph.D. – Multiple Principal Investigators (MPIs)

1. SUMMARY OF PROTOCOL

a. Brief Description of Protocol (Study Design)

This study will examine the effects of combining Varenicline (VRN) and *N*-acetylcysteine (NAC) on neural circuitry function and treating nicotine addiction. Healthy adult nicotine dependent cigarette smokers interested in quitting (n=150) will be randomized to one of four PBO-controlled conditions for 4 weeks: 1) VRN+NAC, 2) VRN+PBO, 3) NAC+PBO or 4) PBO+PBO. Following a baseline fMRI (Day 0) and 1 week of medication, participants will be contingently reinforced for 3 days of smoking abstinence and be fMRI scanned (fMRI-2/Day 10) while nicotine deprived during a resting state and a cue-reactivity (CR) task. Participants will be followed over the next 3 weeks of treatment and clinical variables will be assessed.

b. Specific Aims

Aim 1. Identify the effects of *N*-acetylcysteine (NAC) + Varenicline (VRN) on resting neural network function and behavior. We will examine the individual and combined effects of VRN and NAC on neural circuitry function in humans. We will also identify relations between neural circuitry function and nicotine/smoking self-administration, withdrawal symptom severity and the maintenance of smoking abstinence over the duration of the study.

Aim 2. Examine the effects of NAC+VRN on drug-cue brain response and behavior. We will examine the individual and combined effects of VRN and NAC on cue-induced brain response and behavior in humans, focusing on limbic-striatal and corticostriatal networks. In these experiments we will also identify relations between neural circuitry function and nicotine/smoking self-administration and withdrawal symptom severity and the maintenance of smoking abstinence over the duration of the study.

Exploratory Aim: Participants will complete a Smoking Regulation Relapse task (SRRT) in the laboratory—the effects of VRN+NAC on smoking topography during the SRRT, and on subsequent smoking behavior and relapse will be examined. Whole brain fMRI analyses will be conducted, and relations between fMRI measures and clinical outcomes will be examined.

c. Inclusion/Exclusion Criteria

Inclusion Criteria all subjects:

1. Age 18 - 65
2. English fluency as demonstrated in providing informed consent and the ability to independently follow directions in completing assigned assessments and tasks
3. Functional vision (with corrective lenses as needed) to complete assigned assessments and tasks
4. Current nicotine dependent cigarette smoker with a minimum smoking history of two years
5. Interest in quitting smoking or contemplating a quit attempt in the next 6 months

6. If female, agreement to use birth control (any form of hormonal contraception such as Depo-Provera, daily oral contraception, transdermal patch, or Nuva-ring; intrauterine device; sterilization; or double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm) to avoid pregnancy
7. Refrain from all other tobacco (i.e. dip/chew, cigars, cigarillos) and/or nicotine products (e-cigs, patches, gum, inhalers/sprays) for the duration of study participation

Exclusion Criteria all subjects:

1. Past head injury or primary neurological disorder associated with MRI abnormalities, including dementia, MCI, brain tumors, epilepsy, Parkinson's disease, or demyelinating diseases
2. Any physical or intellectual disability affecting completion of assessments
3. Any contraindication to MRI
4. Positive urine drug screen for illicit substances (other than marijuana or cocaine).
   4a. For those testing positive for marijuana and/or cocaine, meet dependence criteria
5. Current or past psychosis
6. ECT in last 6 months
7. Use of antidepressants, medications with smoking cessation efficacy, or other psychotropic medications in the last month.
8. Positive urine pregnancy test or current breast feeding status
9. Any other condition or concern that in the Investigator's opinion would impact participant safety, compliance with study instructions, or potentially cofound the interpretation of the study results

As part of exclusion criteria #9, participants are specifically asked to not take part in any other research during their active participation in the protocol once eligibility at screening is made through the last visit day of the protocol.

Among females, pregnancy at screening will be exclusionary. Females of childbearing potential must agree to undergo a pregnancy test before the medication trial and prior to each fMRI scanning session. They must further agree to notify the study physician or PA if they become pregnant during the study.

d. Power Calculation and Sample Size

Our primary aim is to evaluate the effects of VRN+NAC on fMRI BOLD signal. We have investigated multiple components of these effects in previous studies: Effects of smoking on cue- reactivity: In a previous study, smoking abstinence increased activation in dlPFC to visual cues in smokers with low negative affect (d =.65); the opposite pattern was observed among smokers with elevated negative affect (d = -1) which resulted in a significant smoking state by negative affect group interaction (d = 1.5). Effects of smoking abstinence on resting-state functional connectivity: Smoking abstinence strengthened rsFC in an amygdala-striatal circuit (rZ's between .56 and .91) and weakened rsFC in the corticostriatal network (rZ = .71). Effects of NAC on rsFC: In our ongoing PBO-controlled NAC fMRI pilot study (N=20), we find that as compared to the PBO group, smokers in the NAC group exhibit stronger rsFC in the

corticostriatal network (rz=.79). Whereas we have not specifically assessed the interactive effects of NAC +VRN on brain function, the studies listed above provide strong support that we will observe significant effects in a sample of 100 participants. The effects of NAC+VRN on neural network function (Aim 1) and brain CR (Aim 2) will be assessed. If we assume that as with our studies of smoking abstinence and NAC, these effects are of medium to large size (e.g. d=.8), with alpha =.05 (1-tailed), a sample of 25 participants in each treatment group will result in power >.90 for detecting effects of treatment on rsFC and CR-BOLD response. In sum, we are confident that the proposed sample size of 100 will be sufficient to test Aims 1a and 2a. *Exploratory Clinical Outcomes*. The clinical outcomes assessed in this study are designed to assess relapse for 3 weeks following a period of monitored abstinence under PBO-controlled medication conditions. Although the study is not specifically powered to detect the secondary hypothesis of an additive effect of VAR and NAC on abstinence from nicotine (2x2 interaction), the stated sample size will allow for the estimation of effect sizes and the precision of the variance in order to inform a subsequent larger study. Based upon completion rates in our prior studies, we anticipate a 15% attrition rate between randomization and the end of the clinical portion of the study; thus, we anticipate that 94 of the 150randomized participants will provide secondary clinical data for analysis (23 in each treatment assignment). Assuming that no additive effect is present and that the NAC/PBO abstinence rate is 10%, we will have 80% power with a type 1 error rate of 5% to detect an abstinence rate of 33% in the VRN group.

2. TRIAL MANAGEMENT

a. List of Participating Enrolling Clinics or Data Collection Centers

The Medical University of South Carolina (MUSC) Departments of Neuroscience and Psychiatry and Behavioral Sciences will be the recruitment site. There will be two primary recruitment sources:

- **Media**: Advertisements will be placed in local print and online media to aid in recruitment. Media advertisement has been routinely used in other substance abuse studies and has been found to be an effective method of recruiting participants.
- **Database Repository:** Dr. Froeliger's laboratory maintains a database repository of subjects that have agreed to be contacted for smoking-related studies. As of 8/1/2015, the repository contains 95 participants that, based upon an assessment within the past 2 years, appear to meet the inclusion exclusion criteria for the current study.

3. DATA MANAGEMENT AND ANALYSIS

a. Data Acquisition and Transmission and Data Entry Methods. Data will be collected by the appropriate individual (research assistant, Co-PIs, Co-I) using standardized paper and electronic forms and will only be identified with the study's ID of the participant. The codes linking the name of the participant to the study ID will be kept confidential in a secured cabinet by the MPIs. Collected forms will be securely transported to the MPIs' data entry center. Survey completion by participants as well as Research Assistants will enter data in REDCap (Research Electronic Data Capture), a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features,

such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). The data analysis plan is outlined in Section D.

b. Quality Assurance. Accuracy and completeness of the data collected will be ensured by weekly review. A 10% random sample of the primary source document will be crosschecked with the database as part of the targeted DSMB audit. If inaccuracies exceed 4%, then a second 10% will be randomly chosen for audit. The REDCap system does not accept outliers, illogical response patterns, etc. The Co-PIs will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection or entry. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined above.

4. Regulatory Issues.

a. Reporting of SAEs

Serious adverse events (SAEs) are defined as events, related or unrelated, that require or prolong hospitalization or result in congenital defects, death, disability, or life threatening event. The Institutional Review Board (IRB) of the Medical University of South Carolina (MUSC) will be immediately informed orally of an SAE as soon as the investigator, co-investigators, or study staff are made aware of it. This information will be communicated orally and by fax immediately to the IRB. A written report will be filed within 72 hours to the IRB, the NIDA Project Officer, and (when applicable) to the FDA. As further clinical information is obtained, follow-up and final SAE reports will be filed with the IRB, NIDA, and the FDA (when appropriate).

b. Reporting of IRB Actions to NIDA

The initial IRB approval will be forwarded to NIDA for review. The protocol will be reviewed annually by the IRB, and annual renewals will be forwarded to NIDA.

c. Report of Changes or Amendments to the Protocol

All proposed changes/amendments to the protocol will be discussed with the NIDA Project Officer prior to implementation. Amendments will then be filed with the IRB. IRB approval of such amendments will be forwarded to the NIDA project officer, and the original amendment approvals will be filed in the primary document manual.

d. Trial Stopping Rules

There are no plans for interim analysis of efficacy data. However, this issue will be discussed further with NIDA and our Project Officer in the event such a formal interim analysis of efficacy is desired. If so, a formal blinded interim analysis of efficacy would be done halfway through the trial to determine if the findings are so efficacious for a particular group that it would be necessary to consider terminating the trial early. In any event, should such an analysis be undertaken, the statistical guidelines, which would be utilized, would indeed be “guidelines” rather than formal rules. It is expected that the DSMB would deliberate, noting in particular whether boundaries had been crossed that would suggest that it would be statistically appropriate terminate the trial. If in fact such a formal interim efficacy analysis is undertaken, it will be utilizing the O’Brien-Fleming (OF) alpha spending function (O’Brien PC & Fleming TR,

1979, “A Multiple Testing Procedure for Clinical Trials,” Biometrics, Volume 35, pages 549-556). The O’Brien-Fleming boundaries would result in an extremely conservative comparison midway through the trial, making it quite difficult to cross a boundary. The advantage of this criterion is that the final analysis is still preserved very closely to the planned 0.05 significance level. This analysis as noted would be done midway through the trial, in particular when approximately one-half of the total sample size has been enrolled and followed.

In addition to the formal analysis for efficacy, safety data will be examined on an ongoing basis by the DSMB. These data will be provided to the DSMB at whatever level of detail they request. Comparisons suggested by the DSMB will be performed in order to make comparisons between treatment groups. Adverse experiences and safety contrasts will be performed as requested by the DSMB when 25%, 50%, 75%, and 100% of the sample is enrolled and followed. DSMB reports will be included as part of each scheduled report to NIDA.

e. Disclosure of Any Conflict of Interest in the DSM

The Principal Investigators, Co-Investigators, and members of the Data and Safety Monitoring Board (DSMB) will report on an annual basis, or more frequently when needed, any conflicts of interest or apparent conflicts of interest to the NIDA Project Officer. On an annual basis, the above individuals will sign a disclosure statement. It should be noted that on an annual basis the investigator fills out a disclosure/conflict of interest questionnaire that is reported and reviewed by the IRB, and when necessary by the university-wide Conflict of Interest Committee.

f. Clinical Trials Registration

Prior to the start of the study, the protocol will be registered on the clinical trials registry (www.clinicaltrials.gov). All serious adverse events will be reported to the MUSC Institutional Review Board (IRB) within 24 hrs. Follow-up of all serious adverse events will be reported as well. All adverse events are reviewed weekly by the Co-PIs and yearly by both the DSMB and the IRB. Any significant actions taken by the local IRB, including significant protocol changes, will be relayed to NIDA. We anticipate the serious adverse event rate to be extremely low. If monitoring indicates otherwise, we will convene a special meeting of the DSMB.

5. TRIAL SAFETY

a. Potential Risks and Benefits for Participants

Potential risks incurred by participants include adverse events related to study medication.

Varenicline: The Varenicline package insert (http://www.pfizer.com/files/products/uspi_chantix.pdf) details adverse events associated with the medication. Specifically, it reports that “the most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.”

Meta-analyses of the four main adverse events in varenicline versus placebo groups in adult trials yielded relative risks (RRs) of 3.21 (95% CI 2.71, 3.80) for nausea, 1.50 (95% CI 1.26, 1.79) for insomnia, 2.79 (95% CI 2.09, 3.72) for abnormal dreams, and 1.20 (95% CI 1.00, 1.45) for headache (Cahill et al., 2009).

While post-marketing anecdotal reports of psychiatric adverse events led to an FDA "black box" warning for varenicline, a meta-analysis of controlled varenicline trials in adults (total n=3091 randomized to varenicline) yielded no significant increase, relative to placebo, in any psychiatric adverse events aside from sleep disturbance (Tonstad et al., 2010). Additionally, a "real world" primary care cohort study including 10,973 smokers prescribed varenicline revealed no evidence of increased risk of self-harm, compared with smokers prescribed other cessation pharmacotherapies (Gunnell et al., 2009).

The informed consent process will be used to thoroughly educate participants about potential medication-related risks (including neuropsychiatric adverse events). This discussion will include thorough review of the FDA "black box" warning for varenicline. Rigorous screening procedures and strict exclusion criteria are designed to exclude potential participants at elevated risk for adverse events. This includes comprehensive psychiatric assessment and evaluation during screening and weekly medication management visits throughout treatment, providing comprehensive, detailed adverse event monitoring. Participants will have access to the study physician 24 hours, 7 days a week for emergencies. Participants experiencing intolerable adverse events will have the opportunity to reduce dose or discontinue medication altogether, while remaining in the study for ongoing monitoring. MPI Gray has admitting privileges for a full spectrum of psychiatric treatment services, including outpatient, day treatment, partial hospitalization, and inpatient programs, in the event that symptom acuity warrants intensive intervention. Urine pregnancy tests will be conducted weekly throughout treatment for female participants.

N-acetylcysteine: Risks to participants include adverse effects from NAC administration. A meta-analysis of studies evaluating long-term oral treatment with NAC for prevention of chronic bronchitis found that NAC was well tolerated, with generally mild, most commonly gastrointestinal adverse effects that did not require treatment interruption (Grandjean et al., 2000). Systemic allergic reactions to NAC have been observed, but only with intravenous administration (Bailey & McGuigan, 1998).

b. Collection and Reporting of AEs and SAEs

All adverse events (AEs) and serious adverse events (SAEs) will be captured on the appropriate adverse event source documents and entered into the database. All SAEs will be reported to DSMB members within 72 hours after they occur. As noted below, collection and reporting of AEs and SAEs will be reviewed upon recruitment/following of 25%, 50%, 75%, and 100% of the study sample, and a report will be prepared on this by the DSMB.

c. Management of SAEs or Other Study Risks

EXCLUSION CRITERIA: The exclusion criteria of this research study are designed to minimize risks to participants. Medical and psychiatric evaluations are extensive at the beginning of the

trial, and these evaluations may be conducted at unscheduled times when clinically indicated for safety.

CONFIDENTIALITY: Participant records are in locked files in locked offices in areas that are locked during holidays, weekends, and non-working hours. Information contained in computer databases is maintained by participant number only, and no specific identifiers are given. No specific or general participant information will be left in the public access areas, and no oral communication regarding participants with identifiers will be made in any public areas. Research staff members have been given extensive training in maintaining confidentiality as well as HIPAA regulations.

MANAGEMENT OF UNANTICIPATED SAEs: After the proper authorities (IRB, NIDA, FDA when appropriate, DSMB members) are notified of any SAE, the principal investigator and co-investigators will convene a meeting to examine clinical events leading up to the SAE to determine what, if any, immediate procedures should be put in place to ensure that a repeat of this SAE does not occur. Guidance will be sought from the NIDA Project Office and DSMB members, and guidance may additionally be issued by the IRB. Any changes in procedures could involve protocol amendments, and such amendments would be subject to the procedures noted above.

6. Trial Efficacy.

a. Plan for Interim Analysis of Efficacy Data

As states above, there are no plans for interim analysis of efficacy data. However, this issue will be discussed further with NIDA and our Project Officer in the event such a formal interim analysis of efficacy is desired. If so, a formal blinded interim analysis of efficacy would be done halfway through the trial to determine if the findings are so efficacious for a particular group that it would be necessary to consider terminating the trial early. In any event, should such an analysis be undertaken, the statistical guidelines, which would be utilized, would indeed be “guidelines” rather than formal rules. It is expected that the DSMB would deliberate, noting in particular whether boundaries had been crossed that would suggest that it would be statistically appropriate terminate the trial. If in fact such a formal interim efficacy analysis is undertaken, it will be utilizing the O’Brien-Fleming (OF) alpha spending function (O’Brien PC & Fleming TR, 1979, “A Multiple Testing Procedure for Clinical Trials,” Biometrics, Volume 35, pages 549-556). The O’Brien-Fleming boundaries would result in an extremely conservative comparison midway through the trial, making it quite difficult to cross a boundary. The advantage of this criterion is that the final analysis is still preserved very closely to the planned 0.05 significance level. This analysis as noted would be done midway through the trial, in particular when approximately one-half of the total sample size has been enrolled and followed.

7. DSM Plan Administration.

a. Responsibility for Data and Safety Monitoring

The MPI, Kevin M. Gray, M.D., will have overall responsibility for safety and data monitoring on a day-to-day basis. The DSMB, as noted below, will provide guidance and input on a scheduled and as-needed basis.

b. Frequency of DSM

Safety data will be reviewed by the Data and Safety Monitoring Board when 25%, 50%, 75%, and 100% of the sample are enrolled and followed. When half the sample has been enrolled and followed, a blind analysis of efficacy data by the Data and Safety Monitoring Board will be conducted only if deemed necessary by NIDA or the Project Officer. Criteria for trial stopping rules as previously described will be evaluated and submitted to the Project Officer. A Data and Safety Monitoring Board Report will be issued to the NIDA Project Officer following each Board meeting.

c. Content of DSM Report

An annual data and safety monitoring report will be written and sent to the NIDA project officer. This information will include, but may not be limited to, a synopsis of the trial, sociodemographic characteristics of subjects accrued, retention and disposition of study participants, quality assurance issues, regulatory issues, and reports of AEs and SAEs. At present, no efficacy report is planned.

8. DSM Board.

A group of MUSC faculty, with shared expertise in smoking cessation research, pharmacotherapy studies, and clinical trials safety and efficacy outcomes methodologies will comprise the DSMB. At present, it is anticipated that the DSMB will initially meet prior to study recruitment (to evaluate plans for data and safety management), with subsequent meetings occurring when 25%, 50%, 75%, and 100% of the study sample is recruited and followed. The DSMB may more frequently should an event require a meeting. At each meeting, issues of conflict of interest, confidentiality, and initial and ongoing study review (including AEs, SAEs, and regulatory issues) will be made. Following each DSMB meeting, communications will be made to the IRB, NIDA, and FDA if required.

9. APPENDIX

List of questionnaires to be used during the study. Questionnaires / Task	Measure
CAARS-SR	ADHS
MINI	intake
PANAS	Affect [State]
TAS-20	Alexithymia
BAI	Anxiety
Caff - 24hrs	behaviors
Log/Diary Review	behaviors
BDI-II	Depression
CES-D	Depression
DTS	Distress Tolerance
CERQ	Emotion regulation
ERQ	Emotional Regulation
UPPS-P	Impulsivity
Basic Demo	intake
Employment Hx	intake
Family Smoking History	intake
30 day TLFB ETOH/drug	intake/behaviors
30 TLFB cigs/other tobacco	intake/behaviors/elig
FFMQ	Mindfulness
CQ	Nicotine
FTND	Nicotine
mCEQ	Nicotine
NWSC	Nicotine
QSU-B	Nicotine
Craving/Temptation to Smoke	Nicotine
Readiness/Confidence to Quit	Nicotine
Smoking Hx Form	Nicotine
Smoking Occasion	Nicotine
WI-PREPARE	Nicotine
WISDM-68	Nicotine
SHAPS	Reward processing/Anhedonia
MRI Screening Form	safety
Penetration of the Blind	Randomization