Study Title: Evaluating *N*-**acetylcysteine as a pharmacotherapy for tobacco disorder**

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TABLE OF CONTENTS

Section	Page numbers
Specific Aims	1
Background and Significance	1
Preliminary Studies	2
Research Design and Methods	3
Protection of Human Subjects	8
References/Literature Citations	12

A. SPECIFIC AIMS

The aim of this study is to assess the effects of *N*-acetylcysteine (NAC) on initial cessation and relapse prevention in adult cigarette smokers. Specifically, this study has the following aims: **Aim 1)** Examine the efficacy of NAC, compared to placebo, in helping smokers achieve three days of continuous abstinence; **Aim 2)** Among those who maintain initial 3-day abstinence, examine the time to relapse over the 8-week intervention between NAC and placebo groups; **Aim 3)** Assess 7-day point prevalence abstinence at the 8-week end-of-treatment study visit in order to obtain effect sizes and estimates of variability to power a randomized clinical trial.

B. BACKGROUND AND SIGNIFICANCE

Cigarette smoking remains the leading cause of preventable death in the United States (US) (1), and approximately 17.8% of the general population are current cigarette smokers (2). While the continued decrease in smoking prevalence is encouraging, initiating and maintaining abstinence remains a substantial hurdle for the vast majority of those with tobacco use disorder (TUD). Fewer than one in ten smokers making an unassisted quit attempt are likely to succeed over the long-term (3-6), making relapse the most likely outcome of any given quit attempt (7). Evidence-based pharmacotherapeutic interventions for TUD have been shown to increase the odds of quitting smoking by two to threefold compared to placebo (8). However, even with the assistance of pharmacotherapy, abstinence rates are still only approximately 40-50% (9-12). This high rate of treatment failure indicates a pressing need to expand smoking cessation pharmacotherapy options to focus not only on promoting initial cessation, but also on the prevention of relapse over a sustained period of time to improve treatment outcomes.

Within the preclinical literature on addiction, glutamate has emerged as a potential pharmacotherapeutic target in the treatment of substance use disorders (SUDs) (13-17). Specific attention has been given to *N*-Acetylcysteine (NAC) for the treatment and management of SUDs due to its actions on the glutamatergic system. Preclinical models have shown that NAC appears to restore normal glutamate signaling and robustly decreases the reinstatement of heroin, cocaine, and nicotine seeking (18-25). Clinical research focused on NAC for SUDs has demonstrated evidence of reduced drug use and/or reduced craving and withdrawal scores under NAC administration among cocaine and cannabis dependent participants (26-30), in addition to tolerability and safety of therapeutic doses. Unfortunately, randomized controlled trials evaluating NAC's efficacy for SUDs have been disappointedly mixed (31-33). Concurrent with the SUD treatment studies described here, preliminary pilot studies have been conducted extending the use of NAC as a pharmacotherapy for TUD.

To this point, four pilot studies have been conducted examining NAC as a pharmacotherapy for TUD. Two studies assessed cigarette/nicotine withdrawal, craving, reward, and neural functional connectivity between NAC and placebo treated participants during brief periods of abstinence (three days) in an outpatient setting. Results from one study found that NAC reduced subjective reward of the first cigarette smoked after abstinence (34), while the

second study (conducted at MUSC; PI Froeliger) found that NAC treated participants were better able to achieve abstinence during the three day period, reported lower craving scores, and demonstrated stronger corticostriatal connectivity (35). Additionally, two pilot clinical trials assessed smoking abstinence during NAC or placebo administration. One study (also conducted at MUSC; PI Malcolm) found a trend towards fewer cigarettes per day for the NAC group, but no benefit on biochemical measures of smoking, craving or withdrawal ratings (19). However, another pilot study demonstrated impressive abstinence rates favoring NAC compared to placebo at the end of 12 weeks of treatment (47% in the NAC group versus 21% in the placebo group) (36).

Currently, NAC's efficacy has not been firmly established and explanation of the mixed results in the literature has not been articulated. One potential hypothesis has been offered to explain negative results and to inform the implementation of NAC as a pharmacotherapy. It has been suggested that the mixed results in the literature may be due to the conditions under which NAC is administered (i.e., during periods of abstinence versus active use of the drug). Studies that have focused on NAC's ability to promote initial cessation have generally demonstrated inconsistent findings. These inconsistencies suggest that NAC appears to have questionable efficacy when administered during periods of active drug use. However, a growing body of evidence suggests that NAC's efficacy may rely on medication administration under conditions of abstinence. NAC may be more efficacious in preventing relapse, and may even *assist* in achieving initial abstinence, but only in the presence of other abstinence-targeted elements (i.e., contingency management, other pharmacotherapies, etc.). Indeed, many of the most robust and positive findings in support of NAC from preclinical models have been in the context of a reinstatement model that mimics relapse vulnerability. Additionally, LaRowe and colleagues (32) found that participants who were abstinent from cocaine at least one week prior to study entry had better outcomes (i.e., longer time to relapse and reduced craving) in the higher dose NAC condition compared to placebo, though no overall effect of NAC was found in this study. Finally, much of the early clinical work demonstrating reduced craving, withdrawal, and drug reward with NAC was conducted through inpatient study designs, where active drug use was prohibited or was experimentally administered (27, 28, 30).

Based on the previous work conducted with NAC, two key gaps in the literature have emerged. First, additional data are needed to understand if NAC is effective in initiating abstinence. Second, is NAC effective as a relapse prevention aid, following a period of abstinence, or does it assist with both? NAC administration during abstinence may be a key feature contributing to positive results, and may also help to explain the negative results. Though this hypothesis has support, it has yet to be directly tested. These questions represent the next steps in the exploration of NAC as a pharmacotherapy for TUD, prior to large-scale evaluation and implementation of NAC among clinical populations. Therefore, this study will focus specifically on NAC as a pharmacotherapy for TUD and will evaluate NAC's influence on initial cessation and relapse prevention over 8 weeks in adult smokers.

C. PRELIMINARY STUDIES

As part of an ongoing collaboration with preclinical and neuroimaging colleagues, Dr. McClure has contributed to translational efforts to better understand NAC's neurobiological mechanisms of action. As part of this collaboration, Dr. McClure was involved in a pilot study that administered NAC, while also reinforcing abstinence from smoking for three days (35). In addition to promising smoking outcomes from this study, it also provided demonstration of feasibility for aspects of this proposed application, including: the ability to successfully reinforce three days of abstinence from smoking and procedural details in reinforcing abstinence (i.e., adequate compensation for abstinence). Within that study, the majority of participants given NAC achieved high rates of abstinence on the second and third days of reinforced abstinence (75% and 100%, respectively). Conversely, those randomized to the placebo condition achieved lower rates of abstinence on the second and third days (12.5% and 25%, respectively). Additionally, Dr. McClure has experience in the conduct of a human laboratory study that reinforced a brief period of abstinence (18 hours) following one week of varenicline titration (37).

Dr. McClure and the research team on this study have experience in safely administering NAC to adult and adolescent study participants. Specifically, the Co-Investigator and medical clinician on this study, Dr. Kevin Gray has extensive experience in conducting medication trials with NAC (FDA IND approval # 78927) and will provide medical oversight and adverse event review for the following protocol. A number of studies have been published by the research team and collaborators to demonstrate adequate safety and tolerability of study medication (19, 26, 32, 33, 35, 38). These studies have largely shown that NAC is well tolerated and no differences were found in the occurrence of adverse events between treatment groups. The PI and research team are prepared to administer NAC or placebo to adult smokers and address all adverse events that may emerge as part of this study protocol. In summary, Dr. McClure and research team have ample experience conducting trials with NAC in substance dependent adults and adolescents, with careful attention to safety and tolerability.

D. RESEARCH DESIGN AND METHODS (including data analysis)

Study Design

This study will assess NAC as both an initial cessation aid and relapse prevention aid. Interested individuals will receive a brief telephone screening to determine if they may be eligible to participate. They will then be scheduled for an initial assessment, consisting of informed consent, followed by completion of self-report questionnaires and semi-structured interviews to determine eligibility. If participants are eligible for the study, they will be asked to return for their training visit. At the training visit, participants will be given instructions on completing remote surveys and counseling in preparation for their target quit date (TQD). Participants will then return for their randomization visit (Day 0), which will occur within 30 days of screening. On Day 0, participants will be randomized to receive double-blind NAC or placebo for eight weeks. Urn randomization procedures will be used. Participants will then be contingently reinforced for abstinence from smoking for three days while taking study medication. Following three days of reinforced abstinence, participants will complete the remaining 8-week treatment intervention. Medication will be terminated at the Week 8 end-of treatment (EOT) visit. Participants will then return at Week 12 (Day 84) for 4-week post-treatment follow-up visit to assess smoking status. The study design is shown in Figure 1. If participants have unexpected conflicts after randomization and cannot keep weekly visit schedule (i.e. transportation issues or visit activity during an extended holiday), then participants may be eligible to complete weekly visits remotely via telephone call. During remote visits, Participants will be called via phone and all protocol procedures will be completed with the exception of a CO sample. Biologic collection (i.e. urine sample) may be obtained with proper planning, the participant may be given the opportunity and supplies required to complete an offsite/at home urine collection should they be willing to follow the proper collection and storage of a sample. Participants will be assessed for AE's, medication compliance, and will complete emailed surveys all within the assigned visit window. A CO sample will be collected at the participants next in-clinic visit. This option will only be used as a last resort for uninterrupted study participation.

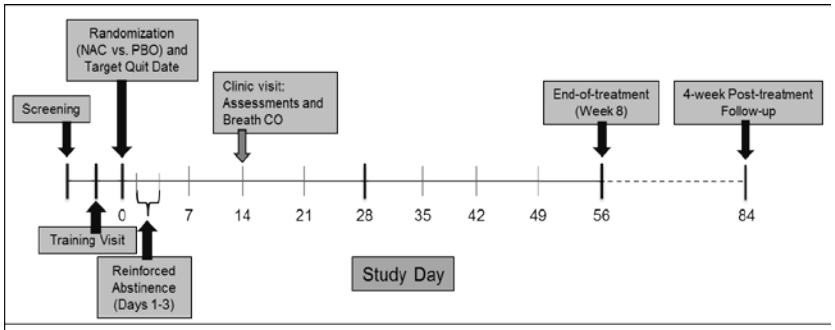

Figure 1. Study design

Assessment

Formal written consent will be obtained from all new participants enrolled in this project. Following the policies of the MUSC Institutional Review Board, written informed consent will be obtained and documented by approved research staff before any study-related procedures are performed. Informed consent will be obtained in a private research office. Each individual may take as much time as they like to decide if they do or do not wish to participate. Following informed consent, participants will complete self-report questionnaires, semi-structured interviews, a medical history, and will also be asked to provide breath and urine samples to assess smoking status, pregnancy status, and to screen for illicit drug use. Dr. McClure (PI) will review all screening material and, in with consultation with Dr. Gray (Co-I and medical clinician) and/or other approved medical clinicians on this protocol, will determine study eligibility for each participant. Additionally, during the assessment visit, participants will be asked to sign a "lifestyle agreement" in which they agree to important aspects of the study procedures (e.g., abstaining from tobacco products and smoking cessation products, engaging in the 3-day quit attempt, and using some form of birth control [female participants only]). This agreement will help to promote adherence to study procedures and provide an additional opportunity to stress the importance of these protocol components. If participants remain interested in the study and meet eligibility criteria, they will be asked to complete morning report surveys through REDCap during the study. The morning report will ask about how many cigarettes were smoked the day prior, if alcohol and/or drugs were consumed, and time of medication dosing (added to survey after Randomization/Day0). Participants will be asked to begin completing morning reports following their screening visit. Links to access the morning report will be sent to participants through their mobile phone and their email address. Participants may complete morning reports on either their smartphone or on a computer.

Training Visit

Participants will return to the clinic to be trained on using a breath carbon monoxide (CO) monitor and prepared for the TQD. Participants will be provided with a breath CO monitor, so that they may take CO readings at home or in a private location of their choosing. Breath CO samples will be taken remotely and videos will be submitted

via REDCap surveys to confirm that the participant is trained and/or prepared for Randomization. Participants may use their personal mobile phones for video submission. If they do not have a smartphone, one will be loaned to them at the training visit. Video submissions may only be completed on a smartphone (cannot be completed on a computer). A survey link will be sent to the participant via text message. Video capture will occur as part of the REDCap survey. Videos are automatically stored on Android smartphones, and participants will be informed of that so they can delete the files, if necessary. Participants using iPhones (and using loaner iPhones from our group) will not have stored videos on their phone and nothing will need to be deleted. At Training, participants will be asked to sign an "equipment honor statement" in which they agree to: 1) return all equipment loaned (as applicable) back to the study team, 2) acknowledge that if equipment is not returned or returned in poor condition it will affect their equipment bonus compensation, and 3) agree to refrain from completing mobile surveys when unsafe to do so (i.e. while driving). This agreement will reinforce importance of returning loaned equipment to study team and promote safe usage of equipment by participants.

Randomization (Day 0)/Abstinence Period

Participants will return to the clinic on Day 0 to receive study medication. Participants will begin taking study medication on Day 1. Day 1 will also be when they abstain from smoking. Participants will be instructed to stop smoking no later than 11:59 pm on the night of their Day 0 visit. Participants will be reinforced contingently for abstinence from smoking on Days 1-3. Two breath CO samples per day will be taken remotely and videos will be submitted via REDCap surveys to confirm smoking status during that time (during Days 1-6 of the study). In order to monitor and confirm medication adherence during the first six days of the study, participants will also record themselves taking their morning and evening medication doses. These videos will be submitted via REDCap surveys at the same time as the CO samples are submitted. If the participant prefers to take the medication before the first prompt of the morning, they will be able to record their medication video and upload the file when completing the survey. Abstinence from smoking is defined as a breath CO of ≤ 6 parts per million (ppm) and/or a 50-75% reduction from the participant's average screening and Day 0 breath CO samples. Participants will continue to complete the morning reports through REDCap through the remainder of the study.

Study Medication

Participants will be randomized to receive either NAC (n=55) or matched placebo (n=55) in double-blind fashion. The dose of NAC will be 2400 mg per day (1200 mg taken twice per day as two 600 mg capsules). This dose was chosen due to its demonstrated tolerability and evidence of efficacy in prior studies (29, 30, 33, 35). Medication will be prepared and packaged by Pitt St. Pharmacy, which has been used previously by our research team. Medication will be provided in pharmacy grade bottles. Bottles of medication will use the Medication Event Monitoring System (MEMSCap™). These caps are child resistant and record a timestamp when the bottle is opened. The MEMSCap system will be used to monitor medication adherence during the trial. The participant and investigator/research staff will remain blinded to medication/placebo condition. Medication for active participants will be stored in locked cabinets in the research space occupied by Dr. McClure (Roper Medical Office Building, 125 Doughty St).

Weekly Study Visits, Follow-Up, and Unscheduled Visits

Participants will return to the clinic for brief weekly visits on Days 7, 14, 21, 28, 35, 42, 49 and 56. At the Day 56 study visit (Week 8, EOT visit), medication will be terminated and a urine sample will be collected to determine smoking status (via urinary cotinine) (39). Participants will be asked to return to the clinic for a 4-week post-treatment follow-up visit at Day 84 (Week 12). During weekly study visits, research staff will review morning report data, perform pill counts, and review data from the MEMSCaps in order to monitor medication adherence. Medication tolerability will be systematically assessed by research staff. Medical clinicians on this protocol will be contacted for consult if any potentially related adverse events are reported. Participants will be encouraged to contact study personnel at any time to address any immediate concerns regarding adverse events. If a participant experiences intolerable medication-related adverse events at any point during the study, a dose reduction to 600 mg twice per day (1200 mg per day) may be undertaken. If a participant is unable to tolerate the reduced doses, the medication will be discontinued, and the participant will continue to be tracked. In previous studies at MUSC using NAC, dose reduction or termination has been rare. In addition to medication assessments, additional self-report smoking assessments will be administered (e.g., craving, withdrawal, smoking satisfaction, cigarettes per day, etc.). Breath CO will be collected at weekly visits, and brief cessation counseling will be conducted. Urine samples will be collected at key time points (Screening, Days 0, 28, 56, and 84) in order to assess for pregnancy, drug use, and cotinine. As stated previously, remote visits may be completed in replace of in-clinic weekly visits. Participants may be asked to return to the study office to complete an unscheduled visit. This visit will be utilized to troubleshoot technology issues, dispense medication, or resolve other unexpected issues that may occur. It is not anticipated that any supplemental data will be collected.

Baseline Screening Assessments

1. **Demographic Data, Locator Information, Smoking History, and General Health Assessment**: Basic demographics, including age, gender, race, and social history will be collected. Participants will complete a locator information form which will be used to contact participants to remind them of study visits. The research team will use several methods of contact to keep in touch with participants. We will ask them to provide us with phone numbers, e-mail addresses, current home and work addresses, and contact information of family and friends who may know how best to reach them. We will also have a Facebook account that we may use to contact participants. The research team will only use private messages to contact participants through Facebook. This information will be kept in a locked cabinet with the protected health information. Additionally, participants will be asked about their smoking history and general health (i.e., current and/or past medical or psychiatric issues, current anxiety, stressors, etc.) to determine eligibility for study procedures.
2. **Mini International Neuropsychiatric Interview for DSM-5** (**MINI**) (40) : The MINI is a brief, structured interview designed to ascertain a current, past, or lifetime history of the major Axis I psychiatric disorders in DSM-5 and ICD-10 and current substance use disorders.
3. **Beck Depression Inventory (BDI**) (41): A self-report depression instrument validated in adolescents and adults. This will be used to monitor depression symptoms at every study visit.
4. **Urine Pregnancy Test**: This will be monitored among female participants to exclude from study participation. This will be conducted before urine drug screen. If the pregnancy test is positive, the urine drug screen will not be performed.
5. **Urine Drug Screen**: This will be used to test for common drugs of abuse (e.g., marijuana, cocaine, opioids).
6. **Fagerström Test for Nicotine Dependence (FTND**) (42): This is a self-rating questionnaire for nicotine dependence. FTND has good reliability, validity and internal consistency.
7. **Timeline Follow-Back** (**TLFB**) (43): The TLFB is a calendar-based instrument that measures daily amounts of drug and alcohol consumption for a specified period of time by patient self-report. Study personnel will administer this instrument. A 30-day calendar will be used at baseline to gather information related to amounts of drug, alcohol, and tobacco use in the past 30 days. The TLFB will also be administered to collect data on cigarettes per day during the active study period.
8. **Readiness to Quit Scale**: This will be assessed on a 10-point scale, ranging from 1 = not ready to quit to 10 = extremely ready to quit.
9. **Generalized Self-Efficacy Scale (GSES)** (44) **and Smoking Abstinence Self-Efficacy** (45): These self-report measures will be used to assess the participant's self-efficacy in general and specially with respect to their ability to resist temptations to smoking in certain settings.
10. **Stages of Change short form** (46): The Stages of Change short form will assess prior quit attempts in the past year lasting for at least 24 hours and whether participants intend to quit smoking within the next 30 days (preparation stage), within the next 6 months (contemplation stage), or are not thinking of quitting (pre-contemplation stage).
11. **The Distress Tolerance Scale (DTS**) (47): This questionnaire is a validated self-report which measures tolerance, appraisal, absorption, and regulation of emotional distress.
12. **Carbon Monoxide Breathalyzer** (*Bedfont*): Breath carbon monoxide (CO) will be collected at screening, during all study visits, and remotely during Days 1-6 to detect residual levels of carbon monoxide from recent cigarette use.
13. **Urinary Cotinine:** Cotinine is a metabolite of nicotine. Quantitative cotinine analysis and qualitative cotinine instant dipsticks will be conducted to validate smoking self-reports and breath CO.
14. **Vital Signs**: Blood pressure and pulse will be monitored to assess medical stability. Height and weight will also be collected.
15. **Questionnaire on Smoking Urges—Brief** (**QSU-B**) (48): Participants will complete this brief form detailing symptoms of nicotine craving. Participants will additionally complete visual analog ratings of current level of craving and maximum & average levels of craving over the last week.
16. **Minnesota Nicotine Withdrawal Scale** (**MNWS**) (49): The MNWS, a DSM IV-based instrument that assesses symptoms of nicotine withdrawal, will be used to track participants' nicotine withdrawal symptoms.

17. **Modified Cigarette Evaluation Questionnaire** (**mCEQ**) (50): The 12-item mCEQ assesses the reinforcing effects of smoking and contains 5 subscales (smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, aversion).
18. **Wisconsin Predicting Patient's Relapse (WI-PREPARE)** (51): The WI-PREPARE is a 7-item scale that predicts relapse to smoking through assessment of nicotine physical dependence, environmental factors, and individual difference characteristics.
19. **UPPS-P Impulsive Behavior Scale: Short version (SUPPS-P)** (52): The SUPPS-S is a 4-point Likert scale, 20-item measure that characterizes impulsive behavior through 5 subscales.
20. **Positive and Negative Affect Scale (PANAS)** (53): This questionnaire is a self-report measure that assesses positive and negative affect through ratings on 20 adjectives (10 positive and 10 negative). Each item is rated on 5-point scale capturing affect over the past 24 hours. This assessment will also be administered at weekly clinic visits and during the three days of reinforced abstinence.

Randomization and Weekly Visit Assessments (Days 0, 7, 14, 21, 28, 35, 42, 49, 56, and 84)

1. **Medication Diary**: Participants will be asked to report adherence with the medication regimen through the morning report survey. These reports will be reviewed at each study visit.
2. **Vital Signs**: Blood pressure and pulse will be monitored at key time points to assess medical stability and monitor for any changes during study participation (Days 7, 28, 56 and 84). Weight will be collected at key time points (Days 28, 56, and 84).
3. **Adverse Events**: Participants will be asked about adverse events at each study visit. This will be done to assess the safety and tolerability of study medication and procedures.
4. **Concurrent Medications Form**: The use of other medications will be monitored and documented at each clinic visit for safety purposes, including medications with known smoking cessation efficacy.
5. **Urine Pregnancy Test**: This will be monitored among female participants to determine if they should be terminated from the study at any point.
6. **Beck Depression Inventory** (**BDI**)
7. **Urine Drug Screen** (Days 0, 28, and 56 only)
8. **Penetration of Blind Assessment:** Participants will be asked if they think they are receiving active study medication or placebo. The research assistant conducting the study visit will also document whether they think the participant is receiving active medication or placebo (Days 7, 28, 56 and 84 only).
9. **Positive and Negative Affect Scale (PANAS)**

Smoking Assessments (Training, Days 0, 7, 14, 21, 28, 35, 42, 49, 56, and 84)

1. **Cigarette/Alcohol/Drug Use Diary**: Participants will complete a daily diary (REDCap survey) of cigarettes per day, alcohol, and drug use during active medication treatment, which will be reviewed at each weekly visit. The TLFB will be administered to collect data only when morning report data are missing for that day.
2. **Questionnaire on Smoking Urges—Brief** (**QSU-B**): Participants will complete this brief form detailing symptoms of nicotine craving. Participants will additionally complete visual analog ratings of current level of craving and maximum & average levels of craving over the last week.
3. **Minnesota Nicotine Withdrawal Scale** (**MNWS**): The MNWS, a DSM IV-based instrument that assesses symptoms of nicotine withdrawal, will be used to track participants' nicotine withdrawal symptoms.
4. **Modified Cigarette Evaluation Questionnaire** (**mCEQ**): The 12-item mCEQ assesses the reinforcing effects of smoking and contains 5 subscales (smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, aversion).
5. **Carbon Monoxide Breathalyzer** (*Bedfont*)
6. **Urinary Cotinine**: Instant urinary cotinine dipstick tests will be conducted at all study visits, while quantitative tests will be conducted on Days 7, 28, 56, and 84.
7. **Readiness and Confidence to Quit Scale** (Day 0)

Mobile Assessments

1. **Cigarette/Other substance use Diary**
2. **Questionnaire on Smoking Urges—Brief** (**QSU-B**)

3. **Minnesota Nicotine Withdrawal Scale** (**MNWS**)
4. **Modified Cigarette Evaluation Questionnaire** (**mCEQ**)
5. **Carbon Monoxide Breathalyzer** (*Bedfont*)

Compensation

Participants will be compensated $40 for screening, $20 for training, and $20 for randomization. They will be compensated $20 for each weekly study visit (7 visits), $50 for the Day 56 end-of-treatment study visit, and $50 for the 4-week post-treatment follow-up visit (Day 84; Week 12). Compensation will be delivered to participants contingent on abstinence from smoking on Days 1-3 ($40 per day, $120 total), and for completing mobile surveys during Days 1-6 ($5 per survey; $60 possible compensation). Participants will also be compensated $1 per completed mobile morning report ($64 possible), and $30 for returning all study devices and accessories in working order. Participants may earn a total of $594 for study participation. All compensation paid to participants will be made in cash and in-person to the participant enrolled; this includes participant's that may qualify for remote visits.

In the event a participant does not return equipment to the study staff or it is returned in poor condition, this will affect their bonus equipment return compensation by not receiving $30.

If an Unscheduled Visit is required during study participation, the participant will be compensated $10 a visit in return for the time and travel demands.

Respondent-Driven Sampling (RDS) will be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Each eligible participant who is enrolled into the study, and agrees to take part in this recruitment assistance, will be given coupons to pass on to other potential participants. A referral will be instructed to call the study team for screening. If that person successfully completes a screening assessment and is enrolled in the study, the participant who referred them can redeem the coupon for $20. Participation in this process is completely voluntary. Participants may earn more than the listed $586 if they chose to participate in respondent driven sampling. An RDS follow-up contact may be utilized to remind participants, whom agreed to future contact, that they are still eligible to participate even if no longer enrolled in the study.

Statistical Analyses

Categorical clinical and demographic variables will be assessed by chi-square tests of independence, while continuous variables will be assessed using Student's *t*-test. In addition to baseline group differences, preliminary analysis of baseline characteristics with tobacco use outcomes of interest will examine significant correlates of abstinence in the study population. Characteristics found to be significantly associated with tobacco abstinence and relapse outcomes will be included as covariates in the initial stages of model development. The primary measure of interest will be the proportion of biochemically confirmed and self-reported 3-day abstinence (defined as twice per day breath CO measures of ≤ 6 ppm or a 75% reduction from the participant's averaged baseline and Day 0 CO samples). The proportion of participants achieving 3-day abstinence will be compared between NAC and placebo treatment groups using logistic regression models (Specific Aim #1). Secondarily, there is great interest in determining if those who achieved 3-day abstinence under NAC treatment were less likely to relapse over the course of eight weeks compared than those who achieved abstinence under placebo treatment (Specific Aim #2). Daily smoking diary data will be used in conjunction with weekly breath CO measures to determine if and when relapse to regular smoking returned during the eight weeks of treatment with the study drug. Based on recommendations for defining treatment failure, relapse will be defined as smoking during seven consecutive days or smoking at least once over two consecutive weeks (54). This definition will account for regular and irregular smoking over the course of the eight-week intervention phase. Cox proportional hazards models will be developed to assess the efficacy of NAC in prolonging abstinence and preventing relapse. Additionally, end of study 7-day point prevalence abstinence will be assessed through the proportion of self-reported and biochemically confirmed 7-day abstinence. Biochemical confirmation for end-of-study abstinence is defined as a negative daily breath CO measures (≤ 6 ppm or 75% reduction from baseline) and a negative urine cotinine measure (<80 ng/mL). The main effect of NAC versus placebo on the proportion of abstinent participants will be assessed using logistic regression models. All stated models will be computed both unadjusted and adjusted for significant covariates and confounders found in the preliminary analysis. All randomized participants will be included in the primary analysis (intent-to-treat; ITT) and participants will be deemed not-abstinent at any missed visit or missing CO measure (drop-out/loss-to-follow up included). In addition to the primary ITT analyses,

additional exploratory approaches (e.g., modified ITT models, per protocol analysis, and completer analysis) will be undertaken as indicated and a sensitivity analysis comparing these models to the ITT model will be completed.

Power and Sample Size. This study is largely focused on obtaining preliminary data to inform and power a larger randomized controlled trial to assess NAC for TUD. However, the proposed sample size (N=110) of this study will allow for adequate power to detect differences between treatment groups for the first two stated aims and hypotheses. This study is powered to assess the hypothesis that NAC, as compared to placebo, will promote greater abstinence from smoking during a 3-day quit attempt at the beginning of an eight week randomized controlled trial. In a pilot trial (N=16) investigating NAC as a cessation aid over three days of reinforced abstinence, Froeliger and colleagues (35) found that the majority of study participants given NAC achieved high rates of abstinence on the second and third days of reinforced abstinence (75% and 100%, respectively) following a target quit date. Conversely, those randomized to the placebo condition achieved lower rates of abstinence on the second and third days (12.5% and 25%, respectively). With a proposed sample size in the current study of 110 participants (55 randomized to each treatment assignment), this number will provide sufficient power (80%) with a type 1 error rate of 5% to detect abstinence rate differences of as low as 20% between those randomized to NAC versus placebo.

Following the initial 3-day reinforced quit attempt, relapse rates will be examined to determine if NAC aids in relapse prevention as compared to placebo. Detectable relapse relates and associated hazard ratios (HR) based on the proposed sample size (N=110) are shown below in Table 1 based on varying relapse rates among the placebo and NAC groups. Including all randomized participants and assuming 70-90% of those randomized to placebo will relapse throughout the duration of the study, we will be sufficiently powered to detect relapse rates as high as 46-73% in those are randomized to NAC (HR=1.8-2.0). Secondarily, we will assess relapse prevention among only those participants who achieved initial abstinence during the initial 3-day period. Assuming 30% of those randomized to placebo and 50% of those randomized to NAC will attain initial abstinence (low initial abstinence); we will have adequate power to detect relapse rates as high as 34-62% (HR=2.4-2.9) in the NAC group (assuming 70-90% relapse in the placebo group). If we achieve 50% and 75% initial 3-day abstinence in the placebo and NAC groups (high initial abstinence), we will have adequate power to detect relapse rates as high as 41-69% (HR=2.3-2.9) in the NAC group.

Placebo Relapse Rate	All Randomized Participants N=110		Participants who achieve three day abstinence (ABS) Low 3 day ABS; n=45		High 3 day ABS; n=70	
	Detectible NAC Relapse Rates	HR	Detectible NAC Relapse Rates	HR	Detectible NAC Relapse Rates	HR
70%	46%	1.98	34%	2.91	41%	2.25
80%	58%	1.86	46%	2.60	54%	2.09
90%	73%	1.76	62%	2.36	69%	1.95

Table 1. Detectable rates of relapse and associated hazard ratios (HR).

Additionally, assuming a conservative study attrition rate of 20%, a randomized sample of 110 participants (88 study completers) will provide sufficient power to detect a 23-29% difference in end-of-treatment (Week 8) abstinence between the two groups (assuming 10-30% abstinence rate in the placebo group). Therefore, 110 randomized participants will provide sufficient power to detect treatment differences for the first two stated hypotheses, and will provide effect sizes and estimates of variability for end-of-treatment abstinence at eight weeks to power a larger randomized controlled trial.

We will aim to recruit 110 enrolled study participants to have sufficient power to detect between group differences, but will plan to increase enrollment (N=120 total participants) to account for data integrity issues in a small number of participants.

Missing Data and Attrition. In order to minimize missing data and study attrition, enhanced communication between research staff and participants will be emphasized. However, these methods do not ensure that all data will be collected and appropriate analysis methods will be employed to accommodate missing data. In keeping with the ITT principle, we will make every effort to continue assessments for the entire course of treatment, even among those who fail to adhere to randomized assignment or stop participating in the study assigned intervention.

E. PROTECTION OF HUMAN SUBJECTS

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics

The PI and research staff have all completed the CITI Human Subjects Research Education Course and all other necessary human subjects training. A total of 110 male and female adult smokers, between 18 and 65 years old, will be enrolled in study procedures (considered enrolled when randomized to medication condition), primarily through media advertisements (i.e. internet, print, radio). We expect that we will need to consent more than 110 participants in order to enroll the estimated sample size for this study. Therefore, we expect to consent 150 participants, but expect 110 of those consented to qualify and be enrolled/randomized into the study.

We will aim to recruit 110 enrolled study participants to have sufficient power to detect between group differences, but will plan to over enroll (N=120 total participants) to account for data integrity issues in a small number of participants. Due to over enrolling, we will also expect to over-consent the proposed 150 and anticipate an increase to 180 consented participants. The inclusion/exclusion criteria are as follows:

Inclusion Criteria

1. Age 18-65
2. Daily smoker for ≥6 months, smoking approximately ≥5 cigarettes per day on average in the past month or must meet the criteria for nicotine dependence
3. Be interested in quitting smoking
4. Willing to engage in a 3-day quit attempt as part of study procedures
5. Willing to abstain from cannabis and other tobacco products during study procedures
6. If female, agreement to use birth control (any form) to avoid pregnancy during study procedures

Exclusion Criteria

1. Any serious or unstable medical/psychiatric disorder (including severe substance use disorders, other than tobacco use disorder) in the past month that may interfere with study performance based on PI judgment
2. Current pregnancy or breastfeeding
3. Current use of medications with smoking cessation efficacy
4. Known hypersensitivity to NAC
5. Use of carbamazepine or nitroglycerin (or any other medication deemed to be hazardous if taken with NAC) within 14 days of study participation.

Targeted/Planned Enrollment Table

Total Planned Enrollment: 120participants

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	3	3	6
Not Hispanic or Latino	45	69	114
Ethnic Category: Total of All Subjects*	120		
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	12	19	31
White	31	48	79
2 or more races	1	1	2
Racial Categories: Total of All Subjects*	45	69	114

Given the NIH definition of children as all individuals below age 18, this study will exclude children. Males and females will be included.

b. Sources of Materials

Research materials obtained from the individual participants include psychiatric and medical diagnoses information, expired air breathalyzer CO tests, urine pregnancy tests (females only), urine drug screen, blood pressure, pulse, craving, and adverse event information. Responses to questionnaires and expired breath CO measures will be submitted remotely through the participant's mobile phone (or loaner mobile phone) and uploaded directly into REDCap. Video capture of participant's breath CO samples and their surrounding area will also be captured remotely. Videos and images of participants will be stored within REDCap, which is a secure, password-protected data management system maintained by MUSC. For data back-up purposes, videos and participant images will also be stored on secured, password-protected servers maintained by the Addiction Sciences Division at MUSC. These files will only be accessed by the PI and designated research staff. Those files will not be linked with the participant's name, but will have their image, surrounding areas, and any other individuals captured within the frame. All precautionary measures will be taken to ensure that data files are not compromised and are available only for the PI and designated research staff to view. Research data will be obtained specifically for research purposes. We will not use existing specimens, records or data.

c. Potential Risks

Adverse events related to study medication

The informed consent process will be used to thoroughly educate participants about potential medication-related risks. Rigorous screening procedures and exclusion criteria are designed to exclude potential participants at elevated risk for adverse events. Specifically, study research staff will carefully assess adverse events with participants at each study visit and will contact the medical clinician immediately with any concerns. Research staff will also review the participant-completed Beck Depression Inventory at each visit. If the BDI results suggest deterioration with depression or other psychiatric conditions, a more comprehensive assessment will be completed, with careful plan to address symptoms (e.g., discontinuation of study medication if indicated, referral for psychiatric treatment if indicated, development of safety plan if indicated, etc.). The study PI and medical clinician will be immediately contacted in the event of acute concerns and will guide the plan for addressing and managing presenting symptoms. 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. Urine pregnancy tests will be conducted weekly throughout treatment for female participants.

Though detailed safety plans are in place for study participants, no serious or severe adverse events or

interactions are expected to occur with NAC. Adverse events related to this medication (e.g., allergic reaction, decreased appetite, gastrointestinal discomfort) are possible and will be assessed carefully throughout the study.

Loss of confidentiality
The research team has established procedures in place to minimize the risk of any confidentiality breach. Participant records are stored in locked files within locked offices in areas that are locked during holidays, weekends, and non-working hours. Information contained in computer databases is password protected, maintained by participant number only, and devoid of specific identifiers. No specific or general participant information will be left in 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.

Nicotine withdrawal
This study involves a three-day period of abstinence. Participants will be asked to remain abstinent for a total of 72 hours. Participants will be daily smokers, and as such, they may experience tobacco/nicotine withdrawal symptoms and/or discomfort during this time. Tobacco withdrawal symptoms may include anxiety, depressed mood, irritability, restlessness, sleep difficulty and strange dreams, increased appetite/weight gain, headaches, tension, difficulty concentrating and general physical discomfort. There are no reports in the current literature of severe physiological or psychiatric consequences resulting from tobacco withdrawal. Participants will be informed of the potential discomfort they may experience during this brief period of abstinence and will be advised to contact research staff if they feel that their withdrawal symptoms worsen during the 72-hour period.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Participants will be recruited from the general community through media advertising (print and online sources). The Medical University of South Carolina (MUSC) Institutional Review Board (IRB) approved Informed Consent (IC) will be obtained prior to the initial assessment. The consent will be explained orally and in the written form, and will be documented by the signature of the participant on the IC. Consent will be obtained in a private interview room so that the participant may ask any questions to the research staff.

Following the respondent-driven sampling model used enhance recruitment of study participants, this study will also 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. This recruitment tool has been approved for use by other studies within our tobacco cessation research group (PIs, Gray and Froeliger). The costs for this program would be shared among study teams who are recruiting for smoking studies and benefit from this program.

Absence of Coercion
Participation in the study is voluntary. Participants will be compensated $20-50 for each successfully completed visit and up to $140 for abstinence during Days 1-3 of the study protocol. Participants will be eligible for a maximum of $594.

The informed consent agreement that will be read to each participant prior to enrollment in the study explains the following:

a. Compensation will be paid at each study visit.
b. Participants may discontinue participation in the study at any point.
c. Withdrawing from the study will not result in any adverse consequences to the participants.

b. Protection against Risk

Research staff will closely supervise participants throughout their enrollment in the study.

a. Loss of confidentiality: Paper-based information will be kept in on-site locked file cabinet(s) designated for study materials. Data collection instruments or forms containing participant names will be stored in

separate secure locations from those instruments or forms containing subject identification (SID) numbers, and both will be stored separately from the master list linking the SID and names. Paper-based information will be accessible only to study personnel who need access to the information for study purposes. All electronic records will be stored on a password protected secure server with access limited only to study personnel who need access to the information for study purposes.

b. NAC: Exclusion criteria are crafted to exclude potential participants at higher risk for adverse effects, including those taking medications with known metabolic interactions with NAC. We will also monitor vital signs and adverse events during weekly medication monitoring visits. Participants will have access to a medical doctor 24 hours, 7 days a week for emergencies. Urine pregnancy tests will be done for female participants before study inclusion and at every study visit during the medication phase (Weeks 1-8). Serious adverse events will be reported to the local IRB, the sponsor, and the FDA.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There may not be direct benefits of this study to participants, though they may reduce or quit smoking with the experimental pharmacotherapy. We are primarily assessing the feasibility of conducting a trial of NAC in cigarette smokers, though we will also explore the clinical effects of this pharmacotherapy on initial abstinence and relapse prevention. Participation in the study may greatly benefit future inquiry into pharmacotherapy for smoking cessation and improving upon FDA-approved medications.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

This study will inform the clinical treatment of smoking by providing preliminary feasibility and efficacy data for NAC for tobacco use disorder in adult, daily smokers. This study will also help to inform clinicians as to how best NAC should be used for smoking cessation (initial cessation aid, relapse prevention aid, or both). These data are vital to further explore the potential efficacy of NAC in promoting abstinence and relapse prevention in a larger, double blind randomized controlled trial.

5. SUBJECT SAFETY AND MINIMIZING RISKS (Data and Safety Monitoring Plan)

All aspects of the study will be run through the MUSC Department of Psychiatry and Behavioral Sciences, where the PI holds an appointment. Consistent with the guidelines of the MUSC IRB, an internal Data and Safety Monitoring Plan (DSMP) will be used. An internal DSMP is appropriate for this trial because: 1) it does not involve a large number of subjects, 2) it does not involve a multi-site trial, and 3) it presents minimal risks to patients.

Guidelines have been developed for managing and reporting of SAEs. Dr. McClure (PI) and Dr. Gray (Co-I) will work as a team to serve as the Program Manager for SAEs. The Adverse Event (AE) Log will be used to document all AEs. If an AE is non-serious (self-limited with no intervention needed), no further action will be necessary. However, in the case of an SAE (unresolved event), an AE follow-up log will be completed. The clinician will then call Dr. McClure and Dr. Gray with initial reports within 24 hours of the start of AE. The clinician will record the information on SAE Notification Form. He/she will forward hard copies of the complete report (SAE Notification Form, Concomitant Medication Log, and AE Log) to Dr. McClure, who will, in turn notify the IRB about the SAE. If the event is “Serious, Unexpected and Associated,” Dr. Gray will complete Food and Drug Administration (FDA) Form 3500A and will forward it to the FDA. Dr. McClure and/or Dr. Gray also will inform the IRB and the study participants about the SAE. In all of these reviews and reports, strict patient confidentiality will be maintained.

Trained research staff will assess any adverse events and will consult with a medical clinician to assess the severity, relatedness, and if further action is required. Clinical stability and medication side effects will be assessed at each study visit during the medication trial. Study medication may be discontinued at any time due to adverse experiences or marked deterioration. A member of the research team and/or the Department of Psychiatry on-call team will be available by pager at all times. Dosage may be decreased at any time. Participants who are experiencing intolerable side effects will be advised to contact a study physician to discuss whether a dosage reduction is indicated. The dose will not be decreased prior to consultation and approval by a study physician. At the end of the study, participants will be referred to the clinician of their choice (primary care or other practitioner) for continued treatment for nicotine dependence.

Circumstances requiring that a patient be terminated from the study are as follows: (1) Development of intolerable side effects not responsive to dosage reduction (though we will encourage participants to remain in the study without medication). (2) Development of physical illness, which would preclude medication ingestion. (3) Development or exacerbation of a psychiatric condition such as suicidal ideation with a plan or onset of psychotic symptoms, which would normally require medication or other therapeutic intervention such as hospitalization. (4) Emergence of another substance abuse problem that needs more intensive treatment (hospitalization). (5) Incarceration for one week or more during the study. (6) Failure to report for medication assessment within fourteen days of the scheduled visit. (7) Pregnancy. In all cases, the research team will make every effort to manage the participant and collect appropriate adverse event outcome data.

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G. CONSULTANTS

N/A

H. FACILITES AVAILABLE

This study will be conducted within the office and research space of the Addiction Sciences Division (Roper Medical Office Building, 125 Doughty St.), which has a private interview and examination room.

I. INVESTIGATOR BROCHURE

N/A

J. APPENDIX

N/A