Study Title: A prospective trial of varenicline and incentives for tobacco cessation in adults

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PROTOCOL TITLE: A prospective trial of varenicline and incentives for tobacco cessation in adults

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1.0 Objectives / Specific Aims

Though tobacco use rates in the United States (US) have been steadily declining over the past several decades, the burden resulting from tobacco continues to be staggering and disparities still exist in tobacco use rates and resulting adverse health effects. Further, rates of tobacco use are two to three times higher among those with co-occurring substance use disorders and psychiatric conditions compared to the general population. In particular, cannabis co-use among tobacco users is exceedingly common and rates of co-use appear to be increasing among US adults. Cannabis use rates, in general, appear to be rising in the US, in large part due to the reduced perception of harm, its perceived and real medical benefits and increasingly relaxed legislation restricting its use. These factors are likely to lead to further increases in cannabis use and may result in continued increases in the co-use of cannabis and tobacco.

The harms resulting from continued tobacco use have been clearly demonstrated and several efficacious treatments exist, yet there still remain important barriers to successful tobacco cessation that must be addressed to improve abstinence rates for sub-populations of smokers. Specifically, the impact of cannabis use on tobacco cessation outcomes is not well understood and may serve as an obstacle to successful tobacco cessation among co-users. The literature on the impact of cannabis co-use on tobacco cessation has been mixed and fraught with limitations, which precludes the development of treatment recommendations for co-users. The studies that have explored this relationship are limited by their methodological variation, lack of biochemical verification to confirm cannabis use, and variations in study samples used. To date, no prospective studies have evaluated the impact of cannabis use and severity on tobacco cessation outcomes. Further, no studies have collected cannabis use changes during tobacco cessation treatment to assess for concurrent reductions, abstinence, or of greater concern, compensatory (i.e., increased) cannabis use.

This proposed study is a prospective 12-week tobacco cessation trial using established methods and outcomes typical of tobacco cessation trials, but specifically recruiting co-users of cannabis to; 1) evaluate the impact of co-use on tobacco cessation (compared to tobacco only users), and 2) assess changes in cannabis use during tobacco treatment. Adult tobacco users (ages 18-40; N=208) who are motivated to quit smoking will be recruited. Cannabis co-users will be oversampled (2:1). All participants will receive a first-line tobacco cessation pharmacotherapy (varenicline) paired with a behavioral intervention to bolster abstinence (contingency management and psychosocial counseling) for 12 weeks, while cannabis use will not be specifically addressed. Biochemical verification and self-reports (through mobile daily diaries) of substance use will be collected throughout treatment. A subset of cannabis-tobacco co-use participants (N = 48) will engage in an additional ecological momentary assessment (EMA) portion of the study (EMA supplement) for granular observation of patterns of co-use.

Specific Aims of the proposed research are:

Aim #1: examine the impact of cannabis co-use on tobacco cessation among co-users compared to tobacco only users.

> ***Hypothesis 1*:** Co-users will have lower rates of 7-day point prevalence abstinence from tobacco at the end of treatment (Week 12) compared to tobacco only users.

Aim #2: Among co-users, assess changes in cannabis use during tobacco cessation treatment.

Hypothesis 2: Co-users with moderate to high severity of nicotine dependence will demonstrate increases in concurrent cannabis use, while lower severity of nicotine dependence will yield no changes in cannabis use.

Exploratory Aim: To assess for a dose-dependent impact of cannabis use severity on tobacco cessation outcomes among co-users.

2.0 Background

A1. The Prevalence and Harms of Cannabis and Tobacco Co-Use. Tobacco use rates have been steadily declining over the past several decades in the United States (US) (1), though the burden resulting from tobacco continues to be staggering (2). Tobacco is the leading cause of preventable disease and mortality in the US and tobacco-related illnesses cost approximately $300 billion per year in the US alone (2, 3). Of concern, the population of tobacco users has evolved in recent years. Disparities in tobacco use rates exist and disproportionately affect those with lower levels of education and income and among racial and ethnic minorities (4). Rates of tobacco use are two to three times higher in those with co-occurring substance use disorders (5-7) and psychiatric conditions (8, 9) compared to the general population. In particular, cannabis co-use among tobacco users is exceedingly common and rates of co-use appear to be rising among adults.

A.1.a. Increasing prevalence of cannabis-tobacco co-use. Cannabis and tobacco are frequently used together (10-19) and co-use may occur in several forms; such as, simultaneous use (cigar wrappers filled with cannabis 'blunts'), sequential use ('chasing' cannabis with tobacco), for substitution purposes (using one when the other is not available), or in an asynchronous manner. While the overall rates of cannabis and tobacco co-use in the US appear to have increased modestly (~18%) from 4.4% in 2003 to 5.2% in 2012 (20), the prevalence of daily cannabis use among daily cigarette smokers has nearly doubled from 4.9% in 2002 to 9.0% in 2014 (21). One out of every 14 daily cigarette smokers (aged 26+) are daily cannabis users, while among those aged 18-25, one out of every five daily cigarette smokers are daily cannabis users. For comparison, one out of every 100 never cigarette smokers are daily cannabis users (21). This increase may be partially explained by the overall increase in cannabis use in the US. Rates of past month cannabis use for adults increased from 10.7% in 2002 to 14% in 2016, with substantial increases occurring among adults aged 26 and over (4% in 2002 to 7.2% in 2016), while use rates among 18-25 year olds remain high (20.8%) (22). Increases in cannabis use prevalence are in large part due to the reduced perception of harm, its perceived and real medical benefits and relaxed cannabis legislation (23-26). These factors are likely to lead to further increases in cannabis use and may result in continued increases in the co-use of cannabis and tobacco.

A.1.b. Harms associated with co-use. Cannabis and tobacco co-use is associated with public health burden in the form of greater prevalence of psychiatric and psychosocial problems (27, 28), additive health risk (29), and lower self-reported ratings of health (30). There are also treatment-related concerns specific to co-use. Though prevalence of co-use is high, there is surprisingly little consensus regarding treatment recommendations and cessation strategies tailored for co-users. Few published studies of co-use treatment interventions exist and all have been pilot/feasibility trials (31-34). While co-use treatment is needed, the degree to which co-use affects treatment success for a single, targeted substance remains in question. Specifically, the impact of cannabis use on tobacco cessation outcomes is not well understood in the literature and may serve as an obstacle to successful tobacco cessation among co-users. Also unknown is the degree to which compensatory substance use (i.e., increased use) occurs as a result of reduction or cessation from the other substance. Though the harms resulting from continued tobacco use have been

demonstrated and several efficacious treatment strategies exist (35-39), there remain important barriers to successful tobacco cessation that must be addressed to improve abstinence outcomes for sub-populations of smokers.

A2. The Impact of Co-Use on Cessation Outcomes. Cannabis use has been associated with an increased risk of nicotine dependence and greater nicotine dependence among co-users (12, 40-43). However, the literature on tobacco cessation success among co-users has been mixed, fraught with methodological limitations, and to date, no **prospective** studies to inform tobacco treatment among co-users have been conducted. Some evidence, including recent studies, suggests that co-use has an adverse impact on tobacco outcomes. Specifically, cannabis co-use has been associated with lower rates of tobacco cessation when compared to non-cannabis users (44-50), lower levels of sustained tobacco abstinence, increased odds of relapse (51, 52), and lower odds of tobacco quit attempts (53).

However, other studies have found no evidence of an adverse impact of cannabis on tobacco cessation (54-59), no differences in tobacco outcomes based on cannabis use frequency (42, 55), no impact on intentions to quit using tobacco (53, 60), and no adverse influence on the beneficial effects of low nicotine content cigarettes (61). This mixed literature on tobacco cessation outcomes supports the need to study co-use with a rigorous, prospective study design to better answer these important public health questions and inform the research and clinical care of tobacco use disorder. Currently, no prospective studies have evaluated the impact of cannabis use and its severity on tobacco cessation, which is a major objective of this proposed study.

A.2.b. Compensatory substance use among co-users. A treatment concern for co-users is the issue of compensatory (i.e., increased) use of the other, non-treated substance, during cessation. Among co-users, there are data exploring compensatory tobacco use during cannabis reduction/cessation (opposite relationship of the proposed study), though findings have been mixed. Some studies have shown compensatory use (increases in tobacco use during cannabis abstinence/reduction) (62-65), while our research group and others have found no evidence of compensatory tobacco use during cannabis cessation (66-68). We have also found individual differences associated with changes in tobacco use among; 1) those who concurrently reduced their cannabis use (69), and 2) those with lower levels of nicotine dependence (70). A recent study among co-users with schizophrenia found that compensatory use of tobacco was most pronounced in the first seven days of cannabis abstinence, but returned to baseline levels by Day 28 of abstinence (71). This study suggests that the relationship between these two substances may be complicated and transient and therefore must be studied with a design that captures changes in use of the non-treated substance. Patterns of compensatory use are important to determine as tobacco cessation could lead to greater cannabis use and associated adverse effects (72-76). There is a dearth of data available to address the issue of transient or sustained compensatory cannabis use and how reliably compensatory use occurs during tobacco treatment.

A3. Addressing Critical Gaps in the Literature. All of the above studies exploring the impact of cannabis use on tobacco outcomes have been secondary analyses or epidemiological studies using community samples. Available data to better understand this relationship are limited, resulting in critical gaps in the literature, which will be addressed by the proposed study. To further illustrate the significance, innovation, and novelty of the proposed work, Table 1 summarizes and compares design features of recent studies (past 8 years) versus what we are proposing here. Listed studies were all conducted among tobacco users and published on the impact of cannabis use on tobacco cessation. As Table 1 suggests, our study design features, in combination, will provide the most comprehensive, well-controlled, rigorous study to date. Additional gaps in the literature are further outlined below.

A.3.a. Excluding co-users from tobacco studies. It is generally standard practice in tobacco cessation trials to exclude for concurrent substance use disorders, which would eliminate most regular cannabis users. Secondary analyses of co-users in tobacco trials are limited by small sample sizes and may not be representative of the co-using population. If cannabis users are included, they are likely infrequent users or are inaccurately reporting use. Broad spectra of co-using populations are not specifically recruited and comparisons to tobacco only controls are not always possible. As such, severity of cannabis use may be an important variable that predicts treatment response, but tobacco trials are not equipped to answer that question. For example, in a study listed above, cannabis co-use was present in 15% of the sample and participants did not meet clinical thresholds for cannabis use disorder (CUD; 56). That study found that cannabis use did not impact tobacco cessation, which could be due to the level of cannabis use severity.

	Design Features (within Tobacco Trials or National Surveys) specific to Cannabis Use Assessment/Collection						Outcome
	Prospective[a]	Biomarkers	Severity[b]	Daily Use	Quant	Related Co-Use[c]	Adverse impact of cannabis
Haskins et al. (2010) (47)			X				Yes
Metrik et al. (2011) (55)			X	X			No
Hendricks et al. (2012) (58)				X			No
Leyro et al. (2015) (59)							No
Rabin et al. (2016) (56)		[Qual]					No
Pacek et al. (2016) (61)		[Qual]		X			No
Schauer et al. (2017) (51)			X				Yes
Weinberger et al. (2018) (52)							Yes
El-Khoury et al. (2018) (50)							Yes
Vogel et al. (2018) (49)							Yes
McClure (proposed)	X	X	X	X	X	X	?

Qual=Qualitative drug test 1x; Quant=quantification of cannabis use, including non-combustibles; [a]=Prospective indicates that the study was designed to assess the impact of cannabis use on tobacco outcomes (*a priori* hypotheses and powered as such); some parent trials were prospective; [b]=severity of cannabis use (at least 2 levels); [c]=data collected on the temporal ordering of use.

Table 1. Comparison of Study Design Features

A.3.b. Insufficient collection of cannabis use data. When co-users are enrolled in tobacco trials, assessment of cannabis use is insufficiently collected, if collected at all, and data are not available to detect changes in use during treatment. It is possible that the successful treatment of tobacco is resulting in an unintended negative effect on cannabis use. However, the collection of cannabis use data during tobacco trials is time-intensive, costly, notoriously challenging (when self-reported), and not the primary outcome, all of which contribute to the limited capacity to collect these data. A strength of the current proposal is the detailed cannabis quantification that will occur daily via mobile surveys (77). We will also quantify combustible (78) and non-combustible cannabis use preparations (edibles, oils, concentrates) throughout the trial.

A.3.c. Patterns of co-use. The temporal ordering and relationship between cannabis and tobacco co-use is also not routinely collected in tobacco trials or national surveys. The degree of relatedness between these substances (i.e., their temporal order, exerting synergistic drug effects when used concurrently or close in time, etc.) is important to capture prospectively as it may impact tobacco cessation success or the likelihood of compensatory use. Our group has recently published on patterns of cannabis-tobacco co-use and the related nature of these substances (79), which will be captured in the proposed study and represents another notable strength of this proposal and contribution to the literature.

A.3.d. Rapidly changing cannabis environment. The landscape of cannabis use has changed dramatically in the US, which may result in a separation of tobacco and cannabis use. Typically, cannabis and tobacco have shared a similar route of administration, potentially contributing to their prevalent co-use (11). Due to changing legislation and commercial availability, there is now massive variation in cannabis products and methods of administration. Edibles, concentrates (e.g., wax, dabs), and vaporizers are increasingly popular and allow for cannabis use through administration methods that do not involve combustion, potentially

distinguishing them from tobacco. Indeed, it has been suggested that the uptake of cannabis vaporizers may lead to lower rates of cannabis-tobacco co-use (80).

A4. Summary/Scientific Premise. The scientific premise of the current application is based on mixed evidence regarding the impact of cannabis use on tobacco cessation and limitations in the current literature, such as methodological variation, lack of biochemical verification to confirm cannabis use status and severity (Table 1), and variations in the study samples used. Currently, no prospective studies have evaluated the impact of cannabis use and its severity on tobacco cessation. Further, granular data are not available to detect compensatory cannabis use during tobacco treatment, which may represent an unintended adverse consequence of successful cessation. This proposed prospective tobacco treatment study focuses on tobacco cessation among cannabis-tobacco co-users and evaluates how cannabis use may serve as a barrier to successful tobacco cessation. The results from this study will be uniquely positioned for public health impact in the treatment of tobacco use disorder among those using cannabis. Co-occurring cannabis use may be adversely affecting tobacco treatment, in which case, it should be standard practice to address cannabis as part of treatment. Alternatively, if cannabis use does not impact tobacco cessation, it may be unnecessary to encourage cannabis cessation in unmotivated co-users, which may be discouraging their engagement in tobacco treatment. This study will be the first prospective examination of cannabis use impact and changes during tobacco cessation and will provide the necessary information to further develop and personalize treatment strategies for co-users. As cannabis use rates continue to increase, the presence of co-users in tobacco cessation trials and presenting in clinical care will continue to be common. Co-users may require tailored and potentially enhanced tobacco treatment and the results from this study will help to guide tobacco treatment in cannabis co-users and provide them with the best chances of successful long-term abstinence.

B. Approach

B1. Study Overview. This proposed prospective tobacco cessation study will evaluate the impact of concurrent cannabis use and severity on tobacco abstinence among co-users and assess changes in cannabis use during treatment. Adult tobacco users (ages 18-40) who are motivated to quit smoking will be recruited. Cannabis co-users will be oversampled (2:1) and will be compared to tobacco only participants (using appropriate propensity score models). All participants will receive first-line tobacco cessation pharmacotherapy (varenicline) paired with a behavioral intervention to bolster abstinence rates (contingency management and psychosocial counseling) for a standard 12-week treatment period. Cannabis use will not be targeted with treatment. This is not a treatment outcome study per se and thus we are not evaluating (with a control group) an intervention. Rather, cannabis use status (co-use vs. not) is our independent variable. Biochemical verification of tobacco and cannabis use will be collected at screening and throughout the 12-week treatment period in addition to daily self-reports of use. Specifically, this study will: 1) examine the impact of cannabis co-use on tobacco cessation among co-users compared to tobacco only users (Aim #1); 2) with the use of frequent measurement, assess changes in cannabis use (among co-users) during tobacco treatment and determine if profiles of changes in cannabis use emerge (i.e., compensatory use, reduction, no change) (Aim #2); and 3) assess for a dose-dependent impact of cannabis use severity on tobacco cessation outcomes among co-users (Exploratory Aim).

It should be noted that while this is not a randomized and blinded study (cannabis co-use status will be known to research staff), it is important to not bias the results of the study. The hypothesis is that cannabis co-use will adversely impact tobacco cessation, but it's important to the scientific integrity of this study to obscure that hypothesis from study participants and manage biases with research staff. Staff will be educated about introducing bias into the study and methods to manage bias in non-randomized and non-blinded trials. For research participants, the aim of the study will intentionally broad and ambiguous to not

overtly influence their behavior and tobacco quit attempt. The title of the study and consent document, therefore, are not as specific as they would normally be to maintain the integrity of this research.

B2. Preliminary Studies.

Rates of co-occurring cannabis use in tobacco trials. Prior and ongoing trials at the Medical University of South Carolina (MUSC) provide indirect data to support the feasibility of recruiting co-using participants. First, in a recently completed tobacco cessation trial (NIDA U01 DA0317779; PI Gray), varenicline was evaluated for safety and efficacy among youth smokers (Mean age=19; SD=1.5; Range=14-21). Among this sample, 59% (93/157 randomized) tested positive for urinary cannabinoids at screening and 25% of those who reported cannabis co-use were regular users (at least 20 of the past 30 days). Second, in an ongoing adult tobacco cessation study (NIDA R34 DA042228; PI McClure; Mean age=41; SD=11.5; Range=23-62), 27% (20/74 randomized) have tested positive for urinary cannabinoids at screening. This co-use rate is lower than the adolescent trial described above, but is consistent with age-related cannabis use trends. Notably, participants are excluded from the adult trial if they are unwilling to reduce or quit using cannabis during the tobacco quit attempt, which may result in lower co-use rates. Finally, another ongoing study is recruiting treatment-seeking cannabis users (NIDA UG3 DA043231; MPI McRae-Clark and Gray), and 38% of the sample thus far have reported being daily co-users of tobacco. None of these trials are explicitly focused on outcomes tested herein, but they do provide assurance of recruitment goals.

Tobacco abstinence among co-users. In the recently completed adolescent varenicline trial described above (U01 DA 0317779), we evaluated differences between participants with baseline cannabis use (positive urine drug screen or self-reported use in the past 30 days) compared to participants with no baseline cannabis use (negative urine drug screen and no self-reported use). Self-reported tobacco use was assessed across study weeks and the percentage of 7-day point prevalence abstinence is shown in Figure 1 (varenicline group only). The overall percentage of tobacco abstinent visits for cannabis use participants was 14.8%, while the percentage of abstinent visits for non-cannabis participants was 29.7% (RR=1.9; 95% CI=0.9-3.7; p=0.06).

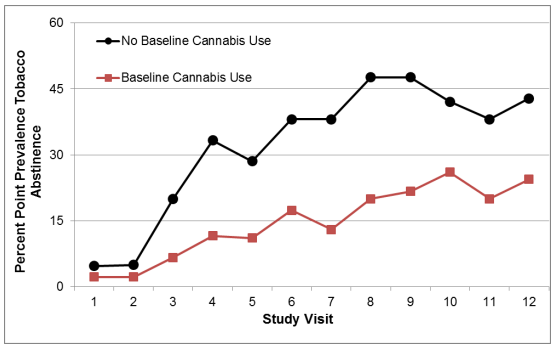


Figure 1.

Severity of cannabis use was explored to assess for dose-dependent effects of cannabis use on tobacco cessation. Since quantitative levels of urinary cannabinoids were not collected, severity categorizations were based on qualitative cannabinoid tests and self-reported days of use (≥20 days of use=severe; positive cannabinoid test and <20 days of use=intermittent; negative cannabinoid test=infrequent/no use). The percent of point prevalence tobacco abstinence in the varenicline-treated group separated by cannabis severity in shown in Figure 2. The risk ratio between no cannabis use and severe cannabis use groups was 4.2 (95% CI=1.4-12.3) and between no use and intermittent use was 1.7 (95% CI=0.9-3.4), suggesting that as baseline cannabis co-use severity escalates, rates of tobacco abstinence decrease.

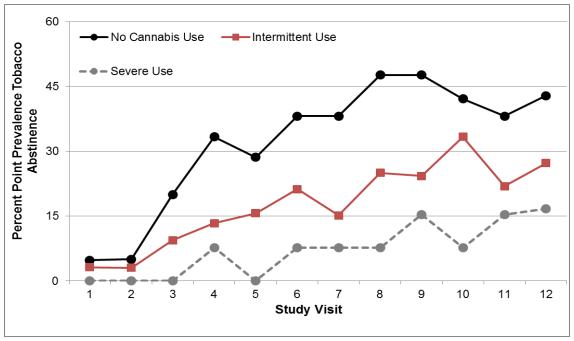


Figure 2.

Finally, we explored cannabis use changes and secondary efficacy of varenicline on cannabis use. Days of self-reported cannabis use in the past week for both varenicline and placebo groups during treatment is shown in Figure 3. Slightly more days of cannabis use were reported in the varenicline group beginning in Week 6 and persisting until Week 12. This result suggests that varenicline did not exhibit secondary efficacy on cannabis use among co-users in this trial, and in fact, cannabis use appeared to increase slightly for the varenicline group later in the trial.

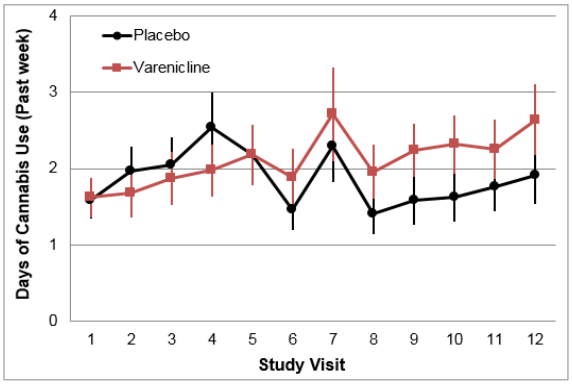


Figure 3.

Age differences in co-users. In the adult tobacco cessation trial described above (R34 DA042228), we compared cannabis co-users with tobacco only participants to assess for differences, on which to inform the control group characteristics for the proposed study. Co-users were similar to tobacco only users on several demographic and tobacco use characteristics, but did differ in age (M=43.4; SD=11.6 for tobacco only users; M=34.7; SD=8.7 for co-users). These data are consistent with epidemiological data on cannabis use prevalence (22), which suggest higher rates of cannabis use for those under the age of 40. To achieve similarity between tobacco only participants and co-users in the proposed study, we will restrict the upper age range for participants to ensure the most appropriate comparison group.

Quit interest in co-users. Cross-sectional survey data collected from our group assessed quit interest and compensatory drug use in co-users (81). Among an online sample (N=182), interest in quitting tobacco was high (7.1±2.9; 10-point scale), while interest in quitting cannabis was low (2.4±2.3; 10-point scale). This study also found that among participants who had ever tried to quit tobacco (80%), half self-reported increases in their cannabis use during the quit attempt. While these data were retrospective, this result further emphasizes the importance of measuring cannabis use changes during tobacco treatment. These data also suggest that the proposed design will be acceptable to co-users given that tobacco treatment will be provided while not addressing cannabis use, as co-users show low interest in cannabis cessation.

3.0 Study Endpoints

Below is a table of the study endpoints and outcomes.

Type	Name	Time Frame	Brief Description
Primary	7-day point prevalence tobacco abstinence at the end of treatment (Week 12)	Final 7 days of treatment (Week 12)	7-day point prevalence abstinence from tobacco at the end of treatment (Week 12) will be assessed via biochemical verification and participant self-report and rates of abstinence will be compared between cannabis co-users and tobacco only controls.
Secondary	Changes in cannabis use during tobacco cessation treatment (among co-users)	Final 4 weeks of study treatment (Weeks 8-12)	Among cannabis co-users, cannabis use rates and amounts during the final 4 weeks of tobacco treatment (Weeks 8-12) will be assessed and

			nicotine dependence will be the primary model predictor.
Other: Exploratory	Cannabis co-use severity on tobacco cessation (among co-users)	Throughout trial participation	Tobacco abstinence and indicators of tobacco reduction (average cigarettes per day, quantitative cotinine, etc.) throughout the trial will be examined as a function of baseline cannabis use severity (determined by days of use in the past 30) to assess for dose-dependent impact on tobacco outcomes based on cannabis use severity.

4.0 Inclusion and Exclusion Criteria/ Study Population

Adult tobacco users (ages 18-40) who are motivated to quit smoking (N=208) will be recruited for the study.

Inclusion criteria:

a) Between the ages of 18 and 40 years old
b) Must be able to understand the study and provide written informed consent
c) Daily cigarette smoker for ≥ 6 months, smoking ≥ 5 cigarettes per day
d) Must submit a breath carbon monoxide (CO) sample of ≥ 7 parts per million (ppm) and/or a positive qualitative cotinine test at the screening visit
e) Be interested in quitting smoking tobacco cigarettes (defined as a 5 or above on a 10-point Likert scale assessing interest in quitting [1=not at all interested, 10=extremely interested])
f) Must be willing to take varenicline for the standard 12-week course of treatment
g) If female, agreement to use birth control (any form) to avoid pregnancy during study procedures

Additional inclusion criteria will be implemented for cannabis co-users, which include:

h) Self-reported use of cannabis on at least 10 out of the past 30 days or submit a positive qualitative urinary cannabinoid test at screening (limit of detection is 50 ng/ml)

Exclusion criteria:

a) Any serious or unstable medical/psychiatric disorder (including severe substance use disorders, other than cannabis or tobacco use disorders) or other significant concern in the past three months that may interfere with study performance, impact participant safety, compliance with study procedures, or potentially confound the interpretation of findings
b) Currently pregnant, lactating, or contemplating pregnancy in the next 6 months
c) Current use of medications with smoking cessation efficacy
d) Use of any medications that would interfere with varenicline (i.e., tafenoquine or quinolones)
e) Regular use of other tobacco or nicotine products other than combustible cigarettes (e.g., smokeless tobacco, electronic cigarettes, etc.) in the past month prior to the quit attempt

5.0 Number of Subjects

A total of 270 participants will be consented with the goal of attaining a total final sample size of 208 (137 co-users, 71 tobacco only users) participants.

6.0 Setting

The research will be conducted at three study sites; 1) the offices of the Addiction Sciences Division at the Medical University of South Carolina, located in the Roper Medical Office Building, 2) Behavioral Health Services (BHS) of Pickens County, located in Pickens, South Carolina, and 3) MUSC Florence. All locations have conducted research studies before and are equipped with several private interview rooms to conduct informed consent and participant visits, a room for conducting physicals and medical histories, bathrooms for collecting urine samples, and storage space for files and study supplies. When possible, remote procedures will be utilized as needed. Participants may engage with study staff at any of the participating sites to complete study procedures. Charleston and Pickens staff will conduct the majority of study procedures with Florence participants.

7.0 Recruitment Methods

This proposed study will enroll 208 participants over the course of 46 months, at a rate of 4.5 participants per month at both participating sites. Several tobacco trials at the Medical University of South Carolina (MUSC) have recruited adolescent and adult cigarette smokers at a rate of 3-5 participants per month (NIDA grants U01DA031779; P50DA16511; R34 DA042228). BHS has experience with recruiting substance using populations into research studies, and similar methods of recruitment will be used in Pickens (and surrounding areas) as are being used in the Charleston area. A recruitment goal of 4.5 enrolled participants per month at both study sites is a reasonable target for the current study.

Our research team has used a number of successful recruitment methods to reach and enroll cigarette smokers and cannabis users. We will implement similar recruitment strategies. Since this study is focused on tobacco treatment, we will employ advertisements that focus on tobacco treatment-seekers, but also will advertise to those using both tobacco and cannabis, especially later in the study when only tobacco-cannabis co-users are needed for enrollment. Several tobacco studies conducted by our research team (in Charleston) fall under the umbrella of "Project Quit," which has general advertisements targeting smokers of all ages and motivation levels. Through marketing of the "Project Quit" brand and continued activity, such as social media educational posts or presence at community events, we maintain a constant presence in the Charleston and surrounding areas, rather than having specific recruitment for one study at a time. This has been a successful recruitment campaign for several research studies. Each study is unique, with its own exclusion criteria, and competition between studies for participants has been minimal. All cigarette smokers interested in research opportunities call or text the same phone number and trained research staff are able to triage interested participants based on their characteristics and interest in quitting. Successful methods of recruitment that have been used previously will be used for this study and include (but are not limited to): print and internet-based recruiting methods (i.e. newspaper advertisements, flyers, billboards, buses, advertisements on Facebook, or other social media platforms, posting on Craigslist, etc.), tv or radio commercials (including streaming services, etc.), primary care, urgent care, and/or hospital or physician referrals (MUSC affiliated clinics or independent medical facilities), postings at local colleges with proper approval(s) (i.e. College of Charleston, The Citadel, Trident Technical Institute, Clemson University, etc.), etc. Potential participants will be directed to a REDCap survey where they can provide us with their contact information. The link to the contact card will be included in our materials such as our website and social media pages. We will also utilize TrialFacts and/or BuildClinical to aid in recruitment for this study (in addition to other potential clinical research organizations that may provide services during the course of

enrollment). TrialFacts, BuildClinical, and other clinical research advertising businesses utilize targeted digital media advertising to recruit participants.

We will also employ additional recruitment methods to research potential study participants. First, we will use ResearchMatch.org to contact potential study volunteers (using IRB approved language) to see if they may be interested and a good fit for this study. We will attempt to search for potential participants near study sites. Second, given the success of cold-contact recruitment used in a current study (Pro105269) and at MUSC generally to reach a wide range of patients that might not otherwise take part in research studies, we propose to use cold contact methods to reach smokers in study location areas. Patient reports will be requested from the MUSC Biomedical Informatics Center [BMIC]). We will ask for searches of the medical record that identify smokers, ages 18-40, within 30-40 miles of Charleston, Pickens, or Florence from MUSC and all regional hospitals. BMIC will gather contact and demographic information (name, phone number, street address, zip code, etc.) for potential study participants, as well as smoking status. All potentially eligible patients will be selected for recruitment unless they have specifically opted out of research communication. Patients' opt-out preferences will be documented in their REDCap Research Contact Form. The study team will not cold contact any patients who already have opt-out preferences noted in their electronic health records.

Additionally, Respondent-Driven Sampling (RDS) will be used to enhance recruitment. 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, is eligible to receive compensation for successful referrals. A referral will be instructed to call the study team to be screened for eligibility. If that person successfully enrolls into the study (i.e., completes the Day 0 visit and begins taking study medication), the participant who referred them can receive $30 in compensation for each eligible participant that is referred and enrolled in the study. The research team has used these methods successfully in the past.

Interested participants will have a brief phone screen conducted to ensure that participants are the appropriate age and are regular tobacco users. Eligible participants will be scheduled for a screening visit. Participants will complete an in-lab screening visit with trained study staff.

8.0 Consent Process

Prior to the initiation of any study procedures, written informed consent and HIPAA authorization will be obtained by the designated research staff. The informed consent process will include a thorough discussion of potential risks associated with participation, including potential adverse effects of study medication.

Potential participants will be given a copy of the IRB-approved consent form and asked to read the document with ample opportunity to take their time in its review. The participant will have the consent documents reviewed with delegated study personnel and have all questions and concerns addressed to their satisfaction. Anyone who cannot demonstrate appropriate understanding of the study or who expresses an unwillingness to participate in the protocol will be ineligible to participate and will be assisted in finding treatment resources. Those who demonstrate understanding of the study and voluntarily agree to participate will be asked to sign the informed consent form and proceed with the screening assessments. As part of the informed consent procedures, participants will be asked to provide or decline consent to be contacted for future studies. Copies of the signed consent documents will be given to the participants for their reference and resource.

We may also use several different methods to complete electronic informed consent, if applicable, that include the following: 1) via MUSC's doxy.me system (teleconsent), or 2) via REDCap electronic consent (e-consent) combined with a video discussion (doxy.me). As a last resort, we will also email the consent document to the participant and conduct the informed consent via video chat (doxy.me). Participants can then email or mail the signed consent back to the research team. Video chat functionality will only be used if all parties have the availability.

All doxy.me signed consent forms will be saved as PDF files within our study records. E-consent via REDCap will be saved with a separate informed consent database. This database will not include any data collected as part of the trial. Using these systems, signatures on the consent form may be obtained electronically via REDCap/doxy.me. In the case that participants mail back hard copies of the consent (in rare instances), those will be stored in locked file cabinets in the offices of research staff. Participants will also be asked to complete a W-9 during the informed consent/e-consent process.

To manage participant bias, the title of the study details in the informed consent document are not as specific as they would normally be to maintain the integrity of this research.

A waiver of consent will be obtained for quality improvement saliva samples. These results will be not used for research purposes.

9.0 Study Design / Methods

Screening Visit: Interested individuals will receive a telephone screening to determine if they may be eligible. They will then be scheduled for a screening visit, consisting of informed consent, followed by a medical history and physical exam by a study clinician, self-report questionnaires, and semi-structured interviews to determine eligibility. If an individual is a patient at MUSC, our medical clinician will have access to his or her medical record and will check for current health issues or medications that may affect safety. At this visit, participants will also see an example mobile diary (on their own mobile device or a loaner smartphone) and complete it in office. Participants will then begin to receive daily diaries, which they will complete every morning to report on their cigarettes smoked, other tobacco use, other drug use, and alcohol used during the previous day. Participants will complete these morning reports daily through their week 12 visit. For those who are eligible, we will employ a training visit separating screening and the start of medication (Day 0) to ensure adequate compliance before the 12-week treatment begins. At this training visit, participants will see an example medication video (on their own mobile device or a loaner smartphone) and complete it in office. After the training visit, participants will begin receiving daily example medication videos, which they will be instructed to complete twice a day to prepare for Day 0. This period constitutes a pre-quit monitoring lead-in prior to the dispensation of medication. The study design is shown in Figure 4.

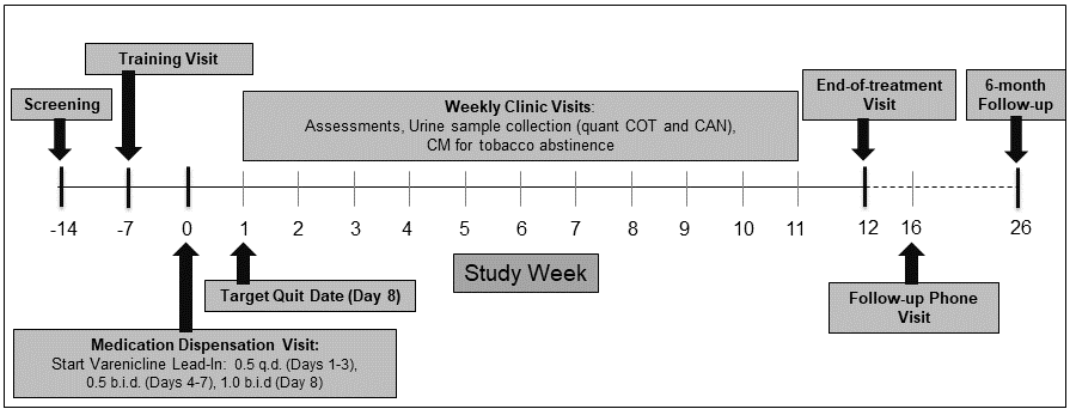


Figure 4.

Training Visit: At this training visit, participants will see an example medication video (on their own mobile device or a loaner smartphone) and complete it in office. After the training visit, participants will begin receiving daily medication videos, which they will be instructed to complete twice a day so as to prepare for Day 0. Participants will complete these medication videos twice a day through their week 12. This period constitutes a pre-quit monitoring lead-in prior to the dispensation of medication. Participants will receive a brief counseling session in preparation for their target quit date (Day 8).

Day 0: On Day 0, participants will be given their first week of varenicline. The standard dose titration schedule will be used, which includes 0.5 mg once per day (q.d.) on Days 1-3, 0.5 mg twice per day (b.i.d.) on Days 4-7, and 1.0 mg b.i.d. starting on Day 8. Dosing of 2.0 mg per day will be maintained for the next 11 weeks. They will be given contact information if they are experiencing adverse events, including an emergency number for after-hour issues with medication. Participants will be encouraged to contact study personnel at any time to address concerns. The medical clinician/Co-I will provide medical supervision for this study and designated medical clinicians will provide oversight for any adverse events. MUSC medical clinician(s) will have the ability to support non-Charleston based site staff with adverse events and other medical concerns remote via telephone, doxy.me, or other HIPAA-compliant, MUSC-IS approved platforms for telehealth. If a participant experiences intolerable medication-related adverse events, a dose reduction to 0.5 mg twice per day may be undertaken (temporary or permanent dose reduction depending on alleviation of symptoms). If the participant is unable to tolerate the reduced dose, the medication will be discontinued, and the participant will continue to be tracked. At this visit, participants will be reminded or retrained on how to upload videos of themselves taking their medication (twice daily) via REDCap. Medication to be used by non-Charleston study sites will be ordered through MUSC and shipped directly to research staff or directly to the participant's home via registered courier. Staff will store medication in a controlled access environment and only accessed by designated staff.

Behavioral strategies will also be used to promote tobacco abstinence. First, psychosocial counseling will be administered at the training visit and Day 0 in preparation for the target quit date (Day 8). During the treatment phase, brief counseling (<5-10 minute) will be provided at all weekly visits by trained research staff and will include motivational enhancement for medication adherence and tobacco cessation. The content of counseling will be skills-based and focused on enlisting social support, recognizing smoking triggers, managing craving/withdrawal/stress, etc. Cannabis use will not be addressed as part of counseling. If the participant expresses a desire to reduce/quit using cannabis, standard information and resources will be provided, but this will be kept minimal to avoid researcher-imposed impact on cannabis use. Participants will be encouraged to pursue desired cessation, but will be reminded that the current study is focused on tobacco cessation.

***Mobile sessions*:** Each morning during the 12-week study (and one week leading up to Day 0), participants will receive a text message and email link to complete their daily diary. Daily diaries will be administered and data will be managed through the Research Electronic Data Capture system (REDCap) (82). Our research team has previously used daily diaries through REDCap (77). Standard questions will be administered regarding substance use that occurred during the prior day (midnight to midnight of the past calendar day).

Weekly Visits (Weeks 1 - 12): Participants will be asked to complete weekly visits for the next 11 weeks. During visits, research staff will review compliance with daily diaries and discuss medication adherence over the past week (assessed through REDCap medication videos, smart bottle caps, daily diaries, and pill counts). Medication tolerability will be systematically assessed, and medical clinicians will be contacted if any potentially related adverse events are reported. Self-report assessments will be administered (e.g., craving, withdrawal, etc.). Brief cessation counseling will be conducted and bonus compensation (i.e.,

contingency management) will be provided based on tobacco abstinence. Vitals will be obtained at weeks 4, 8, 12, or as needed throughout the study (any visit). Urine samples will be collected and separated for: 1) immediate tests conducted by research staff (cotinine, cannabinoids, pregnancy [weeks 4, 8, 12, or as needed], other drugs); and 2) delivery to the MUSC Charleston laboratory for quantitative urinary cotinine and cannabinoid (creatinine-normalized) assay runs. Staff will label and store urine samples (if not in Charleston) to be shipped to MUSC per laboratory protocols. A sub-sample of 10 participants who are cannabis co-users will also be asked to participate in a study addendum that includes the collection of a saliva sample to test for various cannabinoids. Participants will complete their end-of-treatment study visit (Week 12), and a follow-up visit at Week 26. Early termination (ET) visits (in-person or remote) may occur if a participant wishes to withdraw from the study. Week 12 assessments and procedures will be conducted for ET visits, should they occur.

Follow-up Phone Visit (Week 16): During this follow-up visit, participants will be contacted for a brief phone call to assess overall health, as well as current tobacco and cannabis use.

Follow-Up Visit (Week 26): During this final follow-up visit participants will complete self-report questionnaires (e.g., craving, withdrawal, etc.). Daily use of cigarettes, other substances, alcohol, and other tobacco will be gathered during the follow-up period.

Unscheduled Visit (PRN): Participants may be asked to return to the study office for unexpected incidental needs such as addressing a technological concern with the loaned study equipment (phone) or any other issue that cannot be resolved remotely. It is not anticipated that any supplemental data would be collected at these visits and they should take less than 15 minutes to complete.

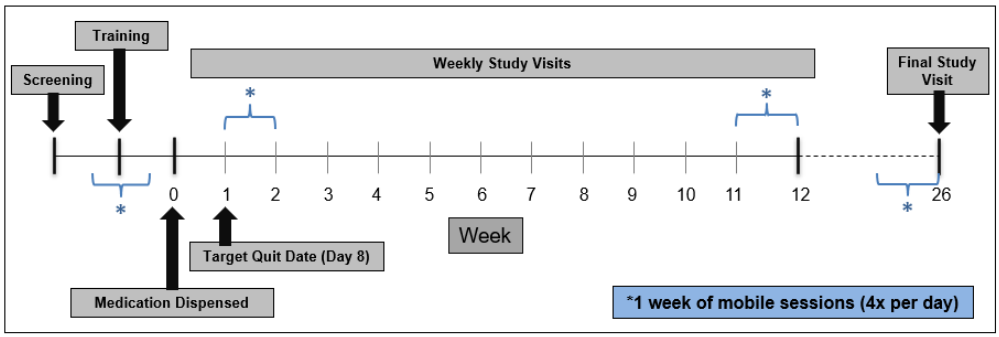
If a participant has an unexpected conflict with attending a visit or the visit must be completely by staff remotely (e.g., transportation issue or travel), arrangements (i.e., phone visit) may be made to remotely complete visit procedures, in order to maintain data collection and study engagement. There is the potential, with proper planning, that participants may be able to complete urine needs at home. Participants will be given proper materials and properly instructed on how to collect/store urine while at home.

Remote Visits: All procedures that can be conducted remotely or through minimized participant contact are possible and will be used as needed (i.e., phone visits, online REDCap surveys, remote consent, detailed medical histories through telehealth platforms). When in-person contact is needed, steps will be taken to minimize contact or the need for a participant to enter a shared research suite (i.e., returning medication bottles in the parking lot, breath CO in their car, at home urine collection procedures, etc.) to comply with any MUSC restrictions in place at that time. At home urine procedures may be conducted (instant-read cotinine, urine drug screen and pregnancy tests), in addition to freezing and returning samples at a later time for laboratory assays (based on supply availability, participant or staff comfort with at home procedures, etc.). If occurring at Day 0, a pregnancy test will be completed prior to medication administration. Participants will be given proper instructions on how to complete the test, and all testing procedures will be performed in real time with participants via video conference (i.e., Zoom, Doxy.me, etc.). Study staff will confirm instant-read cotinine results over video.

Most study procedures can be done remotely, and this will be utilized at the Florence site. Staffing at that site will be minimal and most procedures will be conducted by Charleston or Pickens staff approved and trained on study procedures. Florence staff will engage in human subjects research, data and specimen collection, etc. and will be trained and approved on this study.

Research staff may arrange for taxis to transport participants to research offices when personal transportation is not possible. In rare circumstances, when taxis are not possible, research staff may meet

participants in the community at a public location in order to exchange study supplies (e.g., at home urine samples, medication bottles, or provide study supplies to participants). Safety procedures will be followed if this option is deemed necessary.



EMA Supplement Procedures: In addition to procedures described above, tobacco-cannabis co-using participants (N=48) will be asked to complete 1-week bursts of EMA data collection at four timepoints during the study: 1) baseline/pre-medication (to occur between screening and the Day 0 visit where medication is dispensed), 2) Week 1 (starting at the target quit date and going until Week 2), 3) Week 11 (starting at Week 11 and ending at the Week 12 end-of-treatment visit, and 4) Week 25 (starting at Week 25 and ending at the Week 26 final follow-up visit; see Figure below). The timeframes listed are ideal. The bursts can shift if there are issues such as technology issues or the participant is difficult to contact. The EMA protocol is part of an NIH-funded EMA supplement to the parent study and will be implemented via the ilumivu mEMA platform, which is compatible with Android and iOS devices. During each 1-week EMA burst during the parent study, participants will be asked to complete four semi-random surveys over a 16-hour period (separated into 4-hour time blocks, 1 session randomly prompted in each block).

***Instruments and measures*:** A complete listing of specific instruments/measures is shown below in Table 2 (Assessment Timeline). Cannabis-related instruments will only be administered among co-users.

Screening/Diagnostic Assessments: Detailed demographic information will be collected at screening, which is necessary to inform the propensity score analysis methods. Locator information will be collected and updated throughout the study. Medical and psychiatric assessments will be conducted by designated medical clinicians and trained research staff to ensure eligibility criteria are met.

Biochemical Verification of Tobacco, Cannabis, and Other Substances: At each study visit, a urine sample will be collected and an instant-read urine drug screen will be conducted, which includes a qualitative urinary cannabinoid test (cut-off of 50 ng/ml) to determine cannabis use status, as well as assays for other commonly used substances (amphetamines, opioids, etc.). Urinary cotinine (a metabolite of nicotine) will be the primary indicator of tobacco abstinence (83). Qualitative urinary cotinine will be tested via instant-read, immunoassay test strips for purposes of contingency management. Urine samples will be aliquoted and delivered to the laboratory for determination of quantitative cotinine levels. Abstinence criteria for quantitative cotinine will be set at 80 ng/ml. Urinary quantitative cannabinoid values (11-nor-9-carboxy-Δ9-tetrahydrocannnabinol; THCCOOH) will be tested at MUSC. Urine creatinine will also be obtained, to allow for creatinine-normalized urine cannabinoid levels. Saliva samples will be collected for 10 study participants at one time point. A saliva sample may be collected in addition to other biochemical measures for quality improvement purposes and will not be used for research purposes.

Substance Use Assessments: Several substance use assessments will be conducted throughout the study, including; detailed use history (for all substances), dependence level, motivation to quit (tobacco and cannabis), craving, withdrawal, satisfaction and subjective effects (cannabis and tobacco), and motives for use (full listing in Table 2). TLFB procedures (84) will be used at screening (30-day calendar) to assess the frequency and quantity of tobacco use (cigarettes per day and other tobacco use), cannabis, alcohol and other drug use. In order to determine an individual-specific cannabis unit, cannabis quantification procedures will be conducted at screening and as needed when new methods of cannabis use are endorsed. For plant material-based methods, grams of cannabis will be estimated using a surrogate substance (78).

Participants are asked to show research staff the average amount of cannabis that they use (with the surrogate) for each combustible modality endorsed (e.g., joints, blunts) and report the estimated dollar amount associated with that quantity. The surrogate substance is then weighed on a scale to determine average grams per method. That amount then serves as the individual's standard unit (e.g., "standard blunt") for future reporting. This quantification procedure has been successfully implemented previously (85, 86), is being used in an ongoing study at MUSC (R01 DA038700), and has been shown by our team to improve the predictive validity of clinical outcomes (87). The gram estimation procedure will not work for non-plant based cannabis use methods, which are challenging to quantify. We will quantify these non-combustible methods with techniques used in an ongoing study (R01 DA038700). We will assess times used or hits taken (waxes, dabs, concentrates, lotions), milligrams ingested (edibles, drinks), and milliliters used (oils, tinctures, liquids). We expect that non-combustible methods will continue to evolve and we will modify our procedures accordingly.

Safety Assessments and Medication Adherence: Adverse events will be systematically collected at all visits and will be coded in Medical Dictionary for Regulatory Activities (MedDRA) terms. Medication adherence will be monitored through several methods; pill counts, smart bottle caps, daily self-report of doses taken through the daily diaries, and review of medication videos submitted through REDCap.

EMA measures: EMA items will include 10-30 items assessing cannabis use, tobacco use, and cannabis-tobacco co-use and relevant variables related to co-use relationships. At each EMA session signal, participants will be asked to report whether they have used cannabis, tobacco, or both substances since the previous assessment. Branching logic will be used to administer follow-up items on quantity and frequency of use since the previous assessment, subjective effects, cannabis intoxication, tobacco craving, etc. Each assessment is expected take 1-3 minutes to complete.

Table 2. Assessment Schedule

	SC	T	Treatment Phase													F/U	
Study Week →	SC	T	M	1	2	3	4	5	6	7	8	9	10	11	12	16	26
Informed Consent/Demographics	X																
Locator Form and Updates	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/Psychiatric Assessments																	
Medical History and Physical Exam	X																
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MINI International Neuropsychiatric Interview	X																
Columbia Suicide Severity Rating Scale (C-SSRS) – Clinician Administered	X[a]																
Hospital Anxiety and Depression Scale (HADS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test *(females only)*[a]	X		X				X				X				X		
Biochemical Measures of Substance Use																	
Carbon Monoxide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Drug Screen (instant-read) [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Cotinine (lab assay and instant-read) [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urine Cannabinoids (lab assay)* [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Substance Use Assessments																	
Substance Use History	X																
Timeline Follow-Back	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X
Tobacco																	
Fagerström Test for Nicotine Dependence (FTND)	X						X[f]				X[f]				X		X
Stages of Change - Short Form (Tobacco)	X																
Readiness/Confidence/Interest to Quit Smoking	X	X	X														
Minnesota Nicotine Withdrawal Scale	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Modified Cigarette Evaluation Questionnaire	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Questionnaire on Smoking Urges – Brief	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Smoking Abstinence Self-Efficacy	X						X[f]				X[f]				X		X
Wisconsin Predicting Patient's Relapse	X																
Quit Smoking Methods															X	X	X
Cannabis																	
Cannabis Quantification	X[c]																
Cannabis Use Disorder Identification Test-Revised	X																X
Cannabis Quit Interest	X[d]		X				X[f]				X[f]				X		X
Marijuana Craving Questionnaire	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X
Modified Lyons Battery for Subjective Effects	X		X				X[f]				X[f]				X		X
Marijuana Problems Scale	X		X				X[f]				X[f]				X		X
Cannabis Withdrawal Scale	X		X				X[f]				X[f]				X		X
Marijuana Motives Measure	X																
Patterns of Co-Use Assessment	X		X				X[f]				X[f]				X		X
Acceptability Surveys																	
Medication Acceptability Survey															X		
Participant Satisfaction Survey																	X
Co-Use Treatment Preferences Survey																	X
Medication Safety/Adherence																	
Vital Signs[a] Blood Pressure, Pulse Height [screening] Weight [screening, Weeks 12 and 26]	X		X				X				X				X		X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Adherence																	
Pill counts				X	X	X	X	X	X	X	X	X	X	X	X		
Pillsy cap				X	X	X	X	X	X	X	X	X	X	X	X		
REDCap videos				X	X	X	X	X	X	X	X	X	X	X	X		
Mobile Surveys																	
Daily Diaries	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]		
REDCap Medication Videos EMA Mobile Sessions (ilumivu)	X	X[e]	X[e]	X[e] X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e] X		X

SC=Screening/Assessment; T=Training Visit; M=Medication Dispensation (Day 0); F/U=Post-Medication Follow-Up
[a]=can be completed as needed throughout the study (at any study visit)
[b]=completed at weekly visits when daily dairies are missed
[c]=conducted at screening and then throughout the study when new methods of cannabis use are endorsed; should be completed for any ppt who endorses cannabis use (even if NOT categorized as a co-user)
[d]=administered at screening as part of a cannabis history questionnaire, and then administered alone at subsequent visits
administered daily (diaries) or twice daily (med videos)
[e]=administered daily (diaries) or twice daily (med videos)
[f]=Study assessments completed at Weeks 4 or 8 may be completed at Weeks 5 and 9
[g]=Saliva sample may be collected in addition to other biochemical measures for quality improvement purposes, will not be used for research purposes

*=Saliva sample will also be collected for 10 study participants to assess for cannabinoids

Participant Compensation: Participants will be compensated $40 for the Screening visit and $30 per visit for Training, Day 0, other weekly visits (13 visits) and/or early termination (ET) that occurs at any point other than during the Week 12 window ($50 for Week 12 window visits). They will be compensated $50 for the end-of-treatment visit (Week 12), and $50 for the 6-month follow-up visit (Week 26). Compensation is based on completion of all study procedures. Partial compensation may be given for partially completed study visits. For example, payment amounts for remote visits will be contingent on return of the urine sample to study staff at the next in-person study visit. Compensation will be delivered contingent on tobacco abstinence at weekly visits starting at Week 2 ($20 per visit; $220 possible). Participants will be compensated for completing daily dairies and medication videos during the 12-week treatment phase. Compensation amount for remote surveys and videos will be based on the percentage of videos and morning reports completed over the past week and will be paid at weekly visits. The compensation scheduled based on the percentage of completed sessions is shown to the right ($300 maximum for ≥90% compliance over 12 weeks). Participants may earn a total of $1,050 for study participation and completion of all study procedures.

Medication Videos and Logs (% completed each week)	Payment
90-100% compliance	$25
80-89.9% compliance	$20
70-79.9% compliance	$15
50-69.9% compliance	$10
30-49.9% compliance	$5
<30% compliance	$0

Payment for study visits will be made using a pre-paid debit card, called a ClinCard. It works like a bank debit card and participants may use the card to purchase goods or services everywhere Debit MasterCard is accepted. Participants will be given or mailed a ClinCard at the beginning of the study. Each time they receive payment for participation in this study, the money will be added to the card, as outlined in the payment schedule above. Details of the debit card system are explained on an additional sheet.

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

Additionally, Respondent-Driven Sampling (RDS) will be used to enhance recruitment. 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, is eligible to receive compensation for successful referrals. A referral will be instructed to call the study team to be screened for eligibility. If that person successfully enrolls into the study (i.e., completes the Day 0 visit and begins taking study medication), the participant who referred them can receive $30 in compensation for each eligible participant that is referred and enrolled in the study. The research team has used these methods successfully in the past.

In addition to compensation described above, participants enrolled in the EMA supplement portion of the study will be compensated contingent on completion of EMA surveys. For each 1-week burst of EMA data collection, participants may earn a maximum of $70 for completion of sessions on a sliding scale. A maximum of $280 can be earned over the four, 1-week bursts of EMA data collection.

10.0 Statistical Analysis and Data Management

Analytic Strategy.

Power and sample size. The proposed study is powered to detect a meaningful difference in end of treatment tobacco abstinence between cannabis co-users and tobacco only users. Secondarily, the study will assess the relationship between cannabis use patterns during treatment and nicotine dependence severity in co-users. Specific Aim #1: Examine the impact of cannabis co-use on tobacco cessation outcomes among co-users compared to tobacco only users. Hypothesis 1: Co-users will have lower rates of 7-day point prevalence abstinence from tobacco at the end of treatment (Week 12) compared to tobacco only users. In a cross-sectional survey of national household data (51), tobacco cessation was reported among 65.5% of respondents who endorsed no cannabis use as compared to 21.8% of tobacco cessation in those reporting current cannabis use (Δ=43%). Studies examining the efficacy of varenicline for tobacco cessation (108, 109) noted near 50%-point prevalence abstinence at treatment conclusion (Week 12) in the varenicline-treated group. Finally, in our recently completed adolescent varenicline trial (U01 DA0317779), youth cannabis co-users reported point prevalence tobacco abstinence in 20% of participants at Week 12 and 43% in those who use tobacco only (analysis with all available data). The proposed R01 study intends to apply a successful tobacco treatment (varenicline) paired with contingency management in treatment-seeking smokers. Assuming a similar abstinence rate in tobacco only users (45%) and a successful abstinence rate in participants who are cannabis co-users as compared to the adolescent study (20%; Δ=25%), to achieve 80% power with a 5% type 1 error rate, a sample of 82 participants in the cannabis co-using cohort and 41 in the tobacco only cohort. However, to account for the inclusion of 2 study sites in the design, an additional fixed factor of site will be included in the analytic models. Although we hope that equal proportions of co-users and non co-users present at each site, we understand that the fundamental differences between the Charleston metro area, Pickens County SC, and Florence exist and may cause some correlation between co-use group and study site. Assuming that the proportion of variance in co-use groups due to study site and other covariates may be moderate (R^2=0.25) and that attrition will not exceed 25%, we have adjusted our study sample size to account for this scenario. This increases our randomized sample to a total of 208 (139 cannabis co-users and 69 tobacco only users) accounting for both site correlations with co-use group and anticipated attrition. If site correlations with study outcomes or attrition are lower than pre-specified, our statistical power will exceed 80%. Specific Aim #2: Among co-users, assess changes in cannabis use during tobacco cessation treatment. Hypothesis 2: Co-users with moderate to high severity of nicotine dependence will demonstrate increases in concurrent cannabis use, while lower severity of nicotine dependence will yield no changes in cannabis use. To attain adequate power to assess Aim #2, a within co-use cohort comparison, the study will oversample the cannabis co-use cohort as compared to the tobacco only cohort (2:1). At screening, nicotine dependence will be assessed via the Fagerström Test for Nicotine Dependence (FTND) (92) and categorized accordingly: low nicotine dependence (0-4), medium or high nicotine dependence (5-6; 7-10). Cannabis use during the final 4 weeks of study treatment as compared to baseline use will be assessed among co-users. Based on our preliminary data from an ongoing adult tobacco cessation trial (R34 DA042228), we have nearly equivalent numbers of participants falling into low and moderate/high nicotine dependence categorizations (Mean=4.5; Median=5). Therefore, we anticipate ~40% will have medium/high nicotine dependence. With 208 participants, 139 in the cannabis co-use cohort (104 completers), we will achieve 80% power with a type 1 error rate of 5% to detect a between group cannabis use difference of Cohen's d≈0.6 (Med/High nicotine dependence vs. low nicotine dependence).

Statistical analyses. Demographic, clinical and substance use characteristics will be collected at baseline and tabulated for the overall study cohort and between study groups. Categorical variables will be assessed between groups 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.

Propensity Score Methods: Both cannabis co-using cigarette smokers and tobacco only smokers will be recruited in a 2:1 allocation and all participants will receive varenicline, contingency management, and

psychosocial counseling. Non-randomized trials often suffer from inherent selection bias due to systematic baseline differences in study populations (110). The use of propensity scores has been shown to reduce selection bias and increase parameter estimate precision in non-random designs better than traditional covariate adjustment (111). In the proposed study population, we anticipate a mild, yet systematic difference in baseline factors between cannabis co-users and tobacco only users. Specifically, we expect that age and race (112) may be substantially imbalanced as well as baseline severity of tobacco use and nicotine dependence. To account for such differences, augmented inverse probability of treatment weighting using the propensity score (AIPW) methods will be used to account for observed covariate values (113). This methodology will provide unbiased parameter estimates and standard errors of the average treatment effect even when either the propensity model or outcome model is mis-specified (doubly robust) (114). All observed variables that may potentially influence the self-selection into the co-use group will be included into the calculation of the propensity score (gender, education, motivation to quit, nicotine dependence, social influences, etc.). Prior to model analysis, weighted means of the measured baseline characteristics will be assessed between groups to assess balance. Additionally, weights will be checked for values close to either zero or one and adjustments to the probability model will be made when necessary. Augmented propensity score weighting strategies (AIPW) were chosen as the primary analytic approach as opposed to matching or stratification such that all study participants will be retained in the final analysis and statistical power would be preserved with the proposed sample size.

Primary Study Aims: Aim 1: To assess the difference in the log-odds of abstinence from tobacco at the end of treatment (Week 12) between baseline cannabis co-users compared to tobacco only participants, augmented inverse probability weighted logistic regression models will be developed. The inverse of the conditional probability of being in the cannabis co-use cohort will be included in the model to account for inherent imbalances between study groups and to reduce bias by resembling a randomized controlled trial. In addition to the inverse propensity weights, AIPW methods incorporate a covariate and study site adjusted model for the study group outcome (114). Aim 2: To assess the association of baseline nicotine dependence severity (Med/High nicotine dependence vs. low nicotine dependence) with cannabis use rates during study treatment, generalized linear mixed effects models will be assessed with cannabis use rates and amounts during the final 4 weeks of treatment as the primary indicator of cannabis use severity and nicotine dependence group as the primary model predictor. In addition to grouping by nicotine dependence severity, continuous levels of dependence severity (FTND score) will be modeled to assess possible linear and quadratic relationships between dependence severity and cannabis use. Following examination of the differences in end of treatment cannabis use rates based on baseline nicotine dependence, rates of cannabis use will be assessed by group (nicotine dependence severity) over all weekly study visits to determine if those with increased dependence severity exhibit a different trajectory (slope and pattern) of cannabis use during the entire study treatment. Model-based means and associated standard errors will be used to test group level differences. Exploratory Aim: To assess the relationship between baseline cannabis use severity and tobacco outcomes, generalized linear mixed effects models will be developed with weekly 7-day point prevalence abstinence from tobacco as the primary model outcome. In addition to tobacco abstinence, weekly average cigarettes per day will be examined as an indicator of use reduction differences over time. Longitudinal patterns in tobacco abstinence and use amounts will be modeled through the inclusion of baseline cannabis use severity indicators, study visit, and baseline tobacco use rates as model covariates. Additionally, differential effects over time will be examined with the inclusion of the interaction of cannabis use severity and study visit. Model-based means and associated standard errors will be used to test group level differences across the study treatment.

Secondary Data Analysis: In addition to end of treatment point prevalence tobacco abstinence rates, similar analytic models will be used to assess abstinence rates at the 6-month follow-up visit. Additionally, longitudinal analysis of weekly tobacco abstinence will be assessed using repeated measures logistic regression models using a general estimating equations framework (GEE) (115) and working correlation

structures will be independently compared using the quasi-likelihood under the independence model criterion statistic (116). Similarly, the number of smoking days per week and cigarettes per day will be collected via daily diaries and compared between co-use cohorts using generalized linear mixed effects regression models. Finally, weekly cannabis and tobacco use will be collected to develop group-based trajectory models and time naïve covariates will be used to determine group membership. Additionally, changes in cannabis craving, withdrawal, use, and subjective effects during treatment with varenicline will be examined in the cannabis co-use group. Specifically, changes in cannabis craving, withdrawal (synchronous effects of varenicline) and cannabis use severity (substitution) will be assessed for correlations with changes in tobacco use. Generalized linear mixed effects models will be developed with cannabis use outcomes and the time varying effects of tobacco use as the primary independent variable. Further, noting possible differences in the relationship between tobacco outcomes and combustible/non-combustible cannabis use, model effect modification will be assessed using cannabis use type groupings (primarily combustible vs. primarily non-combustible). All analyses will be conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Missing data and attrition. The study team has procedures in place to minimize missing data and attrition (e.g., reminders, compensation, updated and detailed locator information, etc.); however, these methods do not ensure that all data will be collected. Appropriate analysis methods will be employed to accommodate missing data. Methods of maximum likelihood yield valid inferences assuming ignorable attrition (i.e., attrition is accounted for by covariates or the dependent variable measured prior to dropout). In addition, in keeping with the Intent to Treat Principle, we will make every effort to continue assessments for the entire course of treatment, even among those who stop participating in study procedures.

Data Management. Data will be collected by trained and approved research staff 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 or password-protected data file. Collected study forms will be kept within the office suite of the PI and research staff (Charleston) and within research office suites at participating sites and will not be taken outside of any office buildings. Research staff will enter data into a database management system maintained by MUSC, Research Electronic Data Capture (REDCap). REDCap is a secure, web-based application designed exclusively to support data capture for research studies. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). Direct entry of data by study participants (self-reports) will also be conducted in this study. This is done through a front-end survey interface that allows the participant to enter data on select questionnaires/assessments, but not access any other study records or data in REDCap. A REDCap survey link will be used to collect mobile daily diaries and videos of medication dosing, which are immediately transmitted into REDCap with de-identified subject IDs. Videos are uploaded and stored within REDCap, and not the user's device. Server maintenance will be conducted by Information Technology Specialists at MUSC. The PILLSY platform will house PHI (email and phone number) that is necessary to setup a participant with a smart cap. PILLSY has been vetted by MUSC IS and is approved to house data. The platform is password protected and only accessible by study team members.

For EMA data collection in ilumivu, participants will be assigned a deidentified subject ID, which study staff will keep confidential in a secured cabinet or password-protected data file. After each participant installs the ilumivu app on their personal mobile phone, they will enter a unique code and the app downloads surveys and survey schedules for the participant. Once information is downloaded to the participant's phone, the app is operated offline with no connections to the ilumivu server. Periodically, participants are asked to click a synchronization button to upload the collected data to a secure server. All data are encrypted before being transmitted to the cloud-based storage database. The data are stored in a MariaDB database where the only identifying information associating it with the participant is the unique randomly generated code. Access to the database is gated; entry is only permitted to users entering through the approved route

(cannot be accessed by guessing the URL). Ilumivu, Inc. is an approved vendor with MUSC and is being used with other study protocols. MUSC and ilumivu have signed a terms and conditions document to assure data protection and privacy.

11.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The PI will create a DSMB, comprised of multidisciplinary faculty with expertise in addiction-focused pharmacotherapy and behavioral treatment trials. The DSMB will meet annually (more frequently as needed for emergency situations) to review any AEs related to the study, as well as review of any data management related errors. The board may be called at any point if needed for SAEs, etc. Modification will be made in the procedures and/or the protocol if necessary, based on the findings of the board.

Reports provided to the DSMB on an annual basis will address the following areas: 1) the progress of the research study, including assessments of data quality and participant recruitment, accrual, and retention; 2) review of outcome and adverse event data to determine whether there is any change to anticipated benefit-to-risk ratio of study participation, and whether the study should continue as originally designed, should be changed, or should be terminated; 3) assessment of external factors or relevant information; and 4) review of study procedures designed to protect the privacy of the research participants and the confidentiality of their data. Following review of the annual update on the study, the DSMB will provide a written report that will be submitted annually with the IRB renewal.

Data will be collected by the appropriate individual (PI and/or designated research staff) 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 PI or password-protected data file. Only the PI and designated research staff will have access to these files. Collected forms will be securely transported to the offices of the PI and designated research staff for data entry. Research staff will enter data in REDCap; 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); 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 smartphone application is equipped to transmit data immediately into REDCap. Data are transmitted from study devices and identified through subject IDs. Once data have been transmitted to the secure study server and web portal from the loaner iPhone or participant's personal smartphone, no personal information will be stored on the device. Any information that is stored on the phones will be de-identified. If the loaner iPhone is lost or stolen, devices will be reset immediately.

12.0 Withdrawal of Subjects

Participants will be informed that they may discontinue the study at any time without penalty and that they will be pro-rated for all completed research activities. Participants may also be withdrawn from the study by the PI if it is determined that it is in the participant's best interest (safety concern, requiring intervention) or due to the participant's noncompliance with the protocol.

13.0 Risks to Subjects

The risks associated with participation in this study include adverse events related to study medication (varenicline), nicotine withdrawal, and the potential loss of confidentiality. Potential risk details are

described below and the PI will ensure that all risks are clearly defined for study participants and are thoroughly understood during the informed consent process and throughout the study period.

Adverse Events Related to Study Medication. The informed consent process will be used to thoroughly educate participants about potential medication-related risks. Varencline is the medication being used in this study to support tobacco cessation. Several companies now offer varenicline in the US: 1) Chantix® (from Pfizer in the US: http://www.pfizer.com/files/products/uspi_chantix.pdf]; 2) Apo-varenicline in Canada (authorized for use in the US by the FDA; https://www1.apotex.com/products/us/downloads/mon/apo_var_fct_mon.pdf, https://www.fda.gov/media/150799/download), 3) generic varenicline from Par Pharmaceuticals: https://www.parpharm.com/pdfs/catalog/generic/Varenicline_Tablets_PI_07-2021.pdf), and 4) generic varenicline from Glenmark Pharmacueticals: https://glenmarkpharma-us.com/varenicline-tablets/. The risks associated with study medication (varenicline) are detailed in the informed consent document and will be discussed prior to enrollment. 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." While no serious or severe adverse events or interactions are expected to occur with varenicline, appropriate procedures are in place should participants experience adverse events related to varenicline administration. Rigorous screening procedures and exclusion criteria are designed to exclude potential participants at elevated risk for adverse events related to study medication. This includes comprehensive psychiatric assessment and evaluation to exclude individuals with currently unstable psychiatric and/or medical disorders. Designated medical and research personnel will conduct serial psychiatric and medical evaluations at screening and will be consulted as needed throughout the study to address any concerns that may arise. Comprehensive and detailed adverse event monitoring will be the responsibility of the entire research team. Adverse events related to this medication (e.g., nausea, vomiting, vivid dreams, constipation, neuropsychiatric events) are possible and will be assessed carefully throughout the study. The PI will be immediately contacted in the event of any emergencies and will guide the plan for addressing and managing the situation with the help of the designated medical clinicians on the study team. Participants experiencing intolerable adverse events will have the opportunity to reduce the dose of study medication or discontinue medication altogether, while remaining in the study for ongoing monitoring.

Loss of Confidentiality. There is the risk of breach of confidentiality. The research team has procedures in place to minimize the risk of any confidentiality breach. Participant records are stored in locked files within locked offices, or in password-protected databases. Much of the data collected is de-identified and uses a participant ID. 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. Participants will be informed of these potential risks during the informed consent process and will have the option to leave the study at any point. In specific instances, participant PHI (name, etc.) may be available to other entities, such as for ClinCard registration/payment purposes.

Nicotine Withdrawal. Participants enrolled in the study will receive comprehensive tobacco cessation treatment and may reduce or abstain from tobacco use during the study period. Participants will be daily smokers, and as such, they may experience nicotine withdrawal symptoms and/or discomfort during their quit attempt. Nicotine withdrawal symptoms may include: anxiety, depressed mood, irritability, restlessness, sleep difficulty, strange dreams, increased appetite, headaches, tension, difficulty concentrating and general physical discomfort. There are no reports in the current literature of severe physiological or psychiatric consequences resulting from nicotine 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 study.

Pregnancy. Participants who become pregnant during the trial will be instructed to discontinue study medication and withdrawn from the study. Participants will be encouraged to seek medical attention. The study team will be conducting pregnancy tests on all female participants at every visit to ensure safety. If participants are considering becoming pregnant within the next three months prior to study participation, then they will not be included into the study. We will also ask female participants to agree to use some form of birth control during the study as an additional precaution.

14.0 Potential Benefits to Subjects or Others

This study will have no direct benefit to the research participant.

15.0 Drugs

This study will use varenicline as the study medication (Chantix®, Apo-varenicline, or generic varenicline from Par Pharmaceuticals or Glenmark Pharmaceuticals). Apo-varenicline is a generic version of varenicline that is approved for use in Canada and has been authorized for use in the US by the FDA (https://www1.apotex.com/products/us/downloads/mon/apo_var_fct_mon.pdf, https://www.fda.gov/media/150799/download). Varenicline from Par Pharmaceuticals and Glenmark Pharmaceuticals is approved by the FDA. Study drug will be housed within research office space. The medication will be stored in a controlled environment and locked in a cabinet only assessable by study personnel. Medical personnel will assess each participant to determine if they are suitable for this study and for medication administration.

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