Penn Medicine
University of Pennsylvania School of Medicine

CLINICAL RESEARCH PROTOCOL

The effect of sweet flavoring on the rewarding and reinforcing value of cigarillo use among young adults

Regulatory Sponsor: Janet Audrain-McGovern, Ph.D.
Psychiatry- Center for Interdisciplinary Research on Nicotine Addiction (CIRNA)
3535 Market St.- Suite 4100
215-746-7145

Funding Sponsor: National Institute on Drug Abuse (NIDA)

IRB Protocol Number: 843944

Version # (Date): Version 8 (9.14.2022)

Initial version # (Date): Version 1 (8.18.2020)
Amended: Version 2 (5.27.2021)
Version 3 (7.26.2021)
Version 4 (9.8.2021)
Version 5 (1.7.2022)
Version 6 (4.18.2022)
Version 7 (6.11.2022)
Version 8 (9.14.2022)

Table of Contents

1 Study Summary

Title	The effect of sweet flavoring on the rewarding and reinforcing value of cigarillo use among young adults
Short Title	Cigarillo Flavor (FLAV)
IRB Number	843944
Methodology	This within-subjects study aims to evaluate the subjective rewarding value, the relative reinforcing value, and the absolute reinforcing value of sweet flavored cigarillos across three separate laboratory visits among 86 young adults (ages 18-24 years old) who have previously smoked ≥ 10 or more cigarillos in their lifetime.
Study Center(s)	Single-center
Objectives	To determine whether the subjective rewarding value, the relative reinforcing value, and the absolute reinforcing value of sweet flavored cigarillos are greater than that of non-flavored cigarillos among young adults.
Number of Participants	Eighty-six participants
Main Inclusion and Exclusion Criteria	Main Inclusion: 1. Male and female young adults who are between 18 and 24 years of age who have used ≥ 10 cigarillos in their lifetime. 2. Not currently undergoing smoking cessation treatment or planning to quit smoking cigarettes within the next 30 days. Main Exclusion: 3. Use of less than 10 cigarillos lifetime. 4. Current enrollment or plans to enroll in a tobacco cessation program over the duration of the study. 5. Current use of nicotine replacement therapy or other smoking cessation medication. 6. History of substance abuse (other than nicotine dependence) in the past 12 months and/or currently receiving medical treatment for substance abuse. 7. Alcohol use greater than 25 standard drinks/week. 8. Use of e-cigarettes >15 days in the past 30 days. 9. Women who are pregnant, breast feeding, or planning a pregnancy over the duration of the study period. 10. Serious or unstable disease within the past year (e.g. cancer, heart disease). 11. Lifetime history of schizophrenia or psychosis. **The complete list of study inclusion and exclusion criteria is included within the Characteristics of the Study Population section of this protocol.**

2 Introduction

This document is a protocol for a human research study. This study is to be conducted in compliance with this research protocol, as well as according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization

guidelines), applicable government regulations, and institutional research policies and procedures.

2.1 Background

While cigarette smoking has declined over the past two decades, cigar smoking has increased. Cigar smoking is most prevalent among young adults, with cigarillos accounting for the majority of young adult cigar use. About 13% of young adults 18-24 years old currently smoke cigarillos compared to 3.2% of adults ≥ 25 years of age. Cigarillos are longer, slimmer versions of cigars that typically do not have a filter. Cigarillos expose young adults to comparable or higher levels of nicotine and many of the same toxicants and carcinogens as combustible cigarettes, making cigarillo use in young adults a significant public health concern.

The rapid growth in available flavors has popularized cigarillo use among young adults. Research suggests that young adults prefer flavored to non-flavored tobacco cigarillos, especially those flavored to taste like fruit or other sweets. However, the factors that underlie such preferences have received little attention. Qualitative studies have documented that young adults self-report positive effects associated with flavored cigarillo use, such as a pleasurable buzz, a feeling of being calm and content, and enhanced mood. Behavioral theories conceptualize the choice of sweet flavored cigarillos to non-flavored cigarillos as a reflection of greater rewarding and relative reinforcing value. Surprisingly, only two small studies have formally examined the subjective rewarding and reinforcing effects of sweet flavored tobacco, both focused on e-cigarettes. Data documenting the impact of sweet flavoring on combustible cigarillo use is critical to inform public health and regulatory actions aimed at reducing young adult cigarillo use.

Using validated human laboratory paradigms, the proposed study will break new ground by determining whether sweet flavored cigarillos are more rewarding and reinforcing (relative and absolute) than non- flavored cigarillos among young adults. We anticipate that young adults will have a greater hedonic response to sweet flavored versus non-flavored cigarillos (greater subjective rewarding value), increased motivation to consume sweet flavored versus non-flavored cigarillos (greater relative reinforcing value), and greater consumption of sweet flavored versus non-flavored cigarillos (absolute reinforcing value). These three hypotheses will be tested across three separate laboratory visits among 86 young adults (ages 18-24 years old) who have previously smoked ≥ 10 cigarillos in their lifetime. We will examine whether these indices of abuse liability remain significant while controlling for other factors that may underlie the preference for flavoring. This approach will enable us to provide evidence for the impact of sweet flavored cigarillos on subjective, objective, and behavioral outcomes among young adults.

3 Study Objectives

Primary Aim: To determine whether the subjective rewarding value, the relative reinforcing value, and the absolute reinforcing value of sweet flavored cigarillos are greater than that of non-flavored cigarillos among young adults.

- **H1.** Young adults will report greater subjective rewarding value from a sweet flavored versus a non-flavored cigarillo.
- **H2.** Young adults will "work harder" for sweet flavored cigarillo puffs than non-flavored cigarillo puffs (i.e., higher relative reinforcing value) as measured by a relative reinforcement choice task.
- **H3.** Sweet flavored cigarillos will have higher absolute reinforcing value for young adults than non-flavored cigarillos as measured by a greater number of flavored cigarillo puffs during an ad-libitum session.

Young adulthood is a critical developmental period for the onset of regular tobacco use and the establishment of lifelong use. This will be the first study to: (1) examine the rewarding and reinforcing value (both relative and absolute) of sweet cigarillo flavoring; (2) control for other

factors that may underlie the preference for flavoring; and (3) evaluate these issues in the population with the greatest cigarillo use – young adults. If the hypotheses are supported, the findings would suggest that the availability of sweet-flavored cigarillos increases cigarillo abuse liability, cigarillo use, and the overall high level of tobacco use among young adults. Novel research on cigarillo use and the role of sweet flavoring in abuse liability in this vulnerable population is critical: (1) to highlight the need for cigarillo prevention efforts and to support regulatory action on sweet flavoring; (2) to inform the content of cigarillo use interventions; and (3) to highlight potential public health harms of "grandfathered" flavored cigarillos that will remain on the market even if a ban on cigar flavoring successfully goes into effect.

4 Study Design

4.1 General Design

This within-subjects study aims to evaluate the subjective rewarding value, the relative reinforcing value, and the absolute reinforcing value of sweet flavored cigarillos across three separate laboratory visits among 86 young adults (ages 18-24 years old) who have previously smoked ≥ 10 cigarillos in their lifetime. These three laboratory visits are described below.

4.2 Study Duration

Recruitment/enrollment is anticipated to begin in August 2021 and will continue for 18 months. We estimate that up to 86 participants will have completed the study by February 2023. Visits 1-3 will be completed within a 2-3 week time period. Each participant will be considered "active" until they have completed all three laboratory visits.

4.3 Laboratory Visit 1

Participants will arrive at the BBL at approximately 1:00PM. Eligible participants will document their tobacco use that day (number, time, type) and complete lifetime and past 30 day measures of cigarillo use (flavored, non-flavored, preference), tobacco use history (e.g., cigarette smoking and menthol status), as well as baseline measures of marijuana use, depression, sensation-seeking, cigarillo risk beliefs, exposure to cigarillo flavor marketing, and demographics. Participants will provide a carbon monoxide (CO) sample and a urine sample to conduct urine cotinine analysis.

Subjective rewarding value of cigarillo flavoring. Participants will be exposed to three cigarillos. Participants who are eligible and elect to participate in the study will be required to use the study-provided cigarillos during this portion of the visit in our smoking lab. One cigarillo will be non-flavored, meaning no characterizing flavors were added to the tobacco. Two will contain sweet flavoring (fruit and cream). All three will have the same characteristics, only differing by flavor. Participants will take 2 puffs from the non-flavored cigarillo, the fruit-flavored cigarillo, and the cream-flavored cigarillo. The exposure to the three cigarillos will be separated by 20 minutes each, and the order of the three exposures will be counterbalanced. Order will be stratified by sex and smoking status. After each of the three cigarillo exposures, participants will complete measures of subjective reward. Visit 1 will occur in the afternoon versus the morning to increase the likelihood that participants who smoke cigarettes smoke normally throughout the day and can rate flavoring/no flavoring in the absence of significant withdrawal symptoms. After Visit 1, participants will be scheduled for Visit 2. Participants who use tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) or combustible marijuana will be given instructions to abstain from tobacco products and combustible marijuana 10 hours prior to BBL Visit 2.

4.4 Laboratory Visit 2

Relative reinforcing value of cigarillo flavoring (RRVF). Participants will arrive at the BBL at 1:00 PM and have their CO measured and provide a urine sample to conduct urine cotinine analysis. Participants who use tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) or combustible marijuana will have abstained for 10 hours: CO verified < 10 ppm or < 50% of Visit 1's CO value, cotinine verified < Visit 1's cotinine value. In preparation for the assessment of the RRVF, participants will receive an introduction to a validated behavioral choice paradigm, which permits the evaluation of the preference for sweet flavored cigarillo puffs relative to non-flavored cigarillo puffs. Participants will be introduced to and briefly practice the computer task (described below) whereby they will have the chance to earn points for sweet flavored versus non-flavored cigarillo puffs. The goal is to determine the motivation to use a sweet flavored cigarillo rather than to quantify the reinforcing value of specific flavors. The sweet cigarillo flavor with the highest rewarding value (measured in Visit 1) will serve as the flavor for the assessment of the RRVF.

Participants will then begin the validated choice paradigm to assess the RRVF. Assessment of the RRVF will be accomplished by asking the participants to perform work, in the form of moving a computer mouse to hit targets on one of two computer screens to earn points toward either a sweet flavored or a non-flavored cigarillo. Using a concurrent schedule, participants will be told that they can switch from working on one screen to the other as often as they wish. Participants are instructed to move the computer mouse to have the cursor hit the targets (e.g., either a fruit labelled cigarillo or a cigarillo labeled as plain). Consistent with relative reinforcement paradigms, the reinforcement schedule in the non-flavored cigarillo earning screen will remain constant at a fixed ratio FR-25 (25 targets achieved to earn a point) while the reinforcement schedule for the sweet flavored cigarillo will increase (require more effort) with a progressive ratio schedule of PR-25x over 10 trials, such that 25, 50, 75, 100, 125, 150, 175, 200, 225, and 250 targets will have to be achieved to earn a point.

The computer task will be performed until a participant completes 10 trials and accumulates a total of 10 points from which they will earn either one puff of a non-flavored cigarillo for each point (i.e., up to 10 puffs of a non-flavored cigarillo) or one puff of a sweet flavored cigarillo for each point (i.e., up to 10 puffs of a flavored cigarillo). Participants who are eligible and elect to participate in the study will be required to use the study-provided cigarillos during this portion of the visit in our smoking lab following the RRVF task. Cigarillo puffs will be taken at the end of the procedure to prevent satiation from influencing responding in subsequent trials. RRVF is defined by the breakpoint (highest trial completed across 10 trials to earn puffs for sweet flavored versus non-flavored cigarillo puffs). To ensure that responding in the choice task is based on reinforcer preference rather than departure from the lab, the choice procedure will be followed by a 1- hour wait in the laboratory. After Visit 2 is complete, participants who use tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) or combustible marijuana will begiven instructions to abstain from tobacco products and combustible marijuana 10 hours prior to BBL Visit 3.

4.5 Laboratory Visit 3

Absolute reinforcing value of cigarillo flavoring. The absolute reinforcing value of a sweet flavored cigarillo as measured by an ad-libitum smoking procedure in the lab provides a measure of overall consumption. At this visit, the participant will have the opportunity to self-administer the non-flavored or the sweet flavored cigarillo that they sampled at Visit 1 and chose for the RRVF task at Visit 2. Participants who are eligible and elect to participate in the study will be required to use the study-provided cigarillos during this portion of the visit in our smoking lab. Participants will arrive at the laboratory at 1:00 PM and have their CO measured and provide a urine sample to conduct urine cotinine analysis. Participants who use tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) or combustible marijuana will have abstained for 10 hours: CO verified < 10 ppm or < 50% of Visit 1's CO value, cotinine verified < Visit 1's cotinine value.

The participant will then begin a 90-minute ad-libitum cigarillo smoking paradigm for the assessment of the absolute reinforcing value of a sweet flavored cigarillo. Participants will be taken to a specially ventilated and approved smoking research room equipped with a sofa and table. Participants will be told that they will have a 90-minute laboratory waiting session where they can choose to smoke any of the color coded cigarillos placed on the table in the lab while they periodically complete questionnaires while they wait. Participants will be told that the 90-minute laboratory session will be followed by a 30-minute period of enforced abstinence from tobacco use. The labeled and color coded cigarillos will be placed on a table next to the couch. To limit brand affiliation and expectancy, the cigarillo brand identifier will be covered with tape when we color code the cigarillo for flavoring. A clock will be placed on the table showing minutes elapsed from 90 minutes. The number of cigarillo puffs (sweet flavored versus non-flavored) is the outcome variable, with consumption reflecting the absolute reinforcing value of the flavored cigarillo. Participants will be observed via an observation window by a trained research assistant who will monitor and count the number of cigarillo puffs taken (from each cigarillo) during the 90-minute period. The ad-lib session will be videotaped to independently score the number of puffs taken.

At the end of the visit, a member of the research staff will provide participants with resources on tobacco cessation services. Participants will also review educational and cigarillo cessation prevention materials that explain the study rationale and the importance of cigarillo cessation, especially as it pertains to flavored cigarillos.

5 CHARACTERISTICS OF THE STUDY POPULATION

5.1 Target Population

Participants will be 86 male and female young adults (ages 18-24 years old) who have used $\geq$ 10 cigarillos in their lifetime.

We chose $\geq$ 10 cigarillos/lifetime as a minimum criterion for participation to ensure that cigarillo exposure during the course of the study does not exceed lifetime exposure. As such, completely naïve young adults will not be exposed to cigarillos and regular cigarillo users with well-developed biases in favor of flavored cigarillos will not be included. We will measure cigarillo use history (flavor, non-flavored) and flavor preferences at baseline.

5.2 Accrual

We propose to recruit 100 young adults to ensure 86 participants with complete data at study end. Young adults will be recruited from the community through Internet-based advertisements (e.g., Craigslist, social media) and print advertisements including publications at 2-year and 4-year universities. Young adults who respond to the ads will be prescreened for inclusion and exclusion criteria over the telephone. In order to determine whether the ad respondents meet the inclusion criteria for lifetime cigarillo use, use of cigarillos and other tobacco products (e.g., large and little cigars) will be measured and differentiated through product description, and brand examples of the most popular brands of each product will be provided to aid accurate reporting. Research indicates that the inclusion of brand information increases self-reported cigar use. We will assess whether cigarillos and other cigar products are used as intended or modified for blunting. Cigar products modified for blunting will not count toward the inclusion cutoff for cigar exposure. The number of cigarillo blunts used in the past month and the brand characteristics (untipped, flavor) will be recorded at baseline.

Those meeting initial criteria will be screened at the beginning of Laboratory Visit 1 at the Bio-Behavioral Laboratory (BBL). After providing written informed consent, potential participants will provide a urine sample for a drug screen and a pregnancy test (females only) to determine final eligibility.

To promote participation and retention, participants will receive $240 total for study completion (Visit 1 $55, Visit 2 $60, Visit 3 $75, $40 bonus for completing all assessments).

5.3 Inclusion Criteria

1. Able to communicate fluently in English (i.e., speaking, writing, and reading).
2. Male and female young adults who are between 18 and 24 years of age who have used ≥ 10 cigarillos in their lifetime.
3. Not currently undergoing smoking cessation treatment or planning to quit smoking cigarettes within the next 30 days.
4. Planning to live in the area (or willing to commute) for the duration of the study.
5. Willing to use study-provided cigarillos during three laboratory visits.
6. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent and HIPAA form.

5.4 Exclusion Criteria

Subjects who present and/or self-report with the following criteria will not be eligible to participate in the study:

Smoking Behavior

1. Use of less than 10 cigarillos in lifetime.
2. Current enrollment or plans to enroll in a tobacco cessation program over the duration of the study.
3. Current use of nicotine replacement therapy or other smoking cessation medication.

Alcohol and Drug

1. History of substance abuse (other than nicotine dependence) in the past 12 months and/or currently receiving medical treatment for substance abuse. Counseling and support groups (e.g., Alcoholics Anonymous and Narcotics Anonymous) will not be considered medical treatment for the purposes of this protocol.
2. Current alcohol consumption that exceeds 25 standard drinks/week.
3. Breath alcohol reading (BrAC) greater than .000 at Laboratory Visit 1.
4. Use of e-cigarettes on > 15 days in the past 30 days.

Medical

1. Women, including all individuals assigned as “female” at birth, who are pregnant, breast feeding, or planning a pregnancy over the duration of the study period.
2. Serious or unstable disease within the past year (e.g., cancer, heart disease). Applicable conditions will be evaluated on a case-by-case basis by the Principal Investigator.

Psychiatric

1. Lifetime history of schizophrenia or psychosis.
2. Lifetime history of suicide attempt(s) requiring intervention AND recurring suicidal thoughts or ideations. Evaluated on a case-by-case basis by the Principal Investigator.
3. Current or recent use of anti-psychotic medications.

General Exclusion

1. Past, current, anticipated, or pending enrollment in another research program over the study period that could potentially impact subject safety, study data, and/or the study design as determined by the Principal Investigator.
2. Any medical condition, illness, disorder, adverse event (AE), or concomitant medication that could compromise participant safety or significantly impact study performance as determined by the Principal Investigator. Subjects may be deemed ineligible for any of

the aforementioned reasons at any point throughout the study, as well as during the initial telephone screen.

3. Significant non-compliance with protocol and/or study design as determined by the Principal Investigator. Subjects may be deemed ineligible at any point throughout the study.

5.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the current study will be independent of the participant's work or school activities.

5.6 Subject Recruitment

Participants may be recruited from print, traditional, and social media advertisements, referrals, and/or from our database of previous participants who have agreed to be re-contacted for future studies. All advertising materials will be submitted to the UPENN IRB for approval prior to distribution/posting. Interested participants will first complete a telephone screen to assess their initial eligibility. Participants who are initially eligible will be screened against our registration database to confirm that they are not currently participating in another research study at our Center and have not previously reported a condition or circumstance that would make them ineligible for the current study. These participants who remain initially eligible will then be invited to attend Laboratory Visit 1 at our Center during which they will be presented with the IRB-approved combined informed consent and HIPAA Form and have their final eligibility confirmed. Initially eligible participants will also have the option to review and sign the combined informed consent and HIPAA Form electronically via REDCap prior to completing the rest of Laboratory Visit 1 at our Center.

5.7 Early Withdrawal of Subjects

5.7.1 When and How to Withdraw Subjects

Participants are free to withdraw from the study on their own accord at any time. In addition, participants may be withdrawn by the Principal Investigator at any time per the exclusion criteria listed previously. No follow-up data collection is required for participants who withdraw or are deemed ineligible throughout the study.

6. Study-Provided Cigarillos

6.1 Description

We will use Black and Mild cigarillos (plastic-tipped) given that they are the most popular brand in the marketplace and with young adults. We chose one cigarillo brand to standardize the exposure across participants. Swisher is also a popular cigarillo brand. However, qualitative research suggests that the Swisher brand, especially the untipped variety, is typically used for making blunts, while Black and Mild cigarillos are rarely used for blunting. The flavored Black and Mild cigarillos will include citrus fruit ("Jazz") and cream. We chose two of the most popular sweet flavors on the market and those likely to remain on the market, promoting generalizability and the avoidance of exposure to aversive flavoring. We are not seeking to examine the rewarding and reinforcing value of specific flavors. The non-flavored cigarillo (tobacco without characterizing flavors) will be Black and Mild Classic (plastic-tipped).

We chose to compare sweet flavored cigarillos to non-flavored tobacco cigarillos because they are most popular among young adults. It is important to note that some cigarillos without sweet

characterizing flavors can have significant levels of high-intensity sweeteners, especially if they are untipped or wood-tipped. As such, we chose plastic-tipped Black and Mild Classic cigarillos (0 mg sugar equivalents/cm²) versus Black and Mild Sweets (6.3 mg sugar equivalents/cm²) as the comparator.

6.2 Distribution Schedule

Participant will: (1) sample three cigarillos (2 puffs from each) at Laboratory Visit 1; (2) take a total of 10 puffs from a flavored and/or unflavored cigarillo at Laboratory Visit 2; and (3) typically smoke 0 – 2 cigarillos across a 90 minute ad-lib smoking session at Laboratory Visit 3.

6.3 Receipt, Storage, Dispensing and Destruction

Staff will purchase the cigarillos from previously approved tobacco vendors in Philadelphia. Cigarillos will be maintained at room temperature in a double-locked location (e.g., a locked cabinet in a locked room). A master product accountability log will be maintained throughout the study. All product received, distributed to each unique participant, and destroyed will be documented per standardized product accountability procedures. At the completion of the study, there will be a final reconciliation of cigarillos purchased, dispensed, and cigarillos remaining. This reconciliation will be logged on a study completion reconciliation form. Any notable discrepancies will be investigated, documented, and resolved if possible.

7 Study Procedures

7.1 Telephone Eligibility Screen

Individuals interested in study participation will be screened by a qualified member of the research team to determine initial study eligibility. If the participant meets preliminary eligibility, they will be invited to schedule Laboratory Visit 1 at which their final eligibility will be confirmed.

7.2 In-Center Visits

7.2.1 Visit Reminders

Participants will typically receive study visit reminders 48 to 24 hours prior to their scheduled study visits via phone call, email, and text message (if applicable).

7.2.2 Laboratory Visit 1

During Laboratory Visit 1, (Duration: ~2 hours) participants will:

1. Either hear an informed consent and HIPAA presentation where all the study procedures and institutional policies will be reviewed OR complete a virtual IRB-approved informed consent and HIPAA presentation via REDCap where all the study procedures and institutional policies will be reviewed prior to coming in to complete the remainder of Laboratory Visit 1. The Principal Investigator will determine whether in-person or electronic consent will be collected based on University COVID-19-related guidelines. The in-person consent procedures will proceed as follows: the combined informed consent and HIPAA form will be read verbatim. All participant questions will be answered as appropriate after which the combined informed consent and HIPAA form will be completed (signed and dated) by both the participant and a qualified member of the research team. The electronic consent process will involve the following procedures:
    a. The participant will be required to view the entire combined informed consent and HIPAA form on REDCap prior to signing the document. Upon completing their reading of the consent, the participant will be offered the opportunity to indicate if they have any questions and a staff member will call the participant to complete a

consent discussion via the telephone. All participant questions will be recorded and answered as appropriate after which the combined informed consent and HIPAA form will be completed (virtually signed and dated) by both the participant and a qualified member of the research team.

b. The staff will print a signed copies of this completed record and provide one copy to the participant and save one copy for our records.

2. Confirm the accuracy of information (i.e., name, address, phone number, email [if applicable], date of birth, age, gender, ethnicity, and race) provided during the initial Telephone Eligibility Screen.
3. Complete a UDS (at least 30ml [two tablespoons] of urine). The UDS will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol and Drug). Participants who test positive for any exclusionary medications or recreational drugs per this protocol will be deemed ineligible.
    a. The UDS sample will also be used for urine cotinine analysis.
4. Female participants only: Self-administer a CLIA-waived urine pregnancy test. Female participants are advised that participation of pregnant women in this study is prohibited and that they may withdraw at any time.
5. Perform a BrAC assessment to control for alcohol consumption. Participants with a BrAC greater than 0.000 at Laboratory Visit 1 will be ineligible.
6. Perform a CO breath assessment and collect self-report smoking behavior over the past 24 hours to control for prior tobacco exposure.
7. Answer questions about use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month.
8. Complete measures of Demographics, Smoking History (e.g., duration, rate, regular and/or menthol), FTND (Fagerstrom Test of Nicotine Dependence), and HONC (Hooked on Nicotine Checklist)
9. Complete a Medical History Form with a member of the research team to review for applicable contraindications, including psychiatric exclusions, previously listed under Inclusion and Exclusion Criteria (section 4.3 and 4.4).
10. Complete a baseline concomitant medication review (if applicable).
11. Complete questionnaires:
    a. Adverse Events Form (Open-Ended AEs)
    b. Depression, sensation-seeking, risk beliefs, cigarillo advertising and marketing exposure
12. Use study-provided cigarillos during a session in our smoking lab (required). During this smoking task, participants will sample two puffs from each of three cigarillos. Sampling of each cigarillo will be separated by 20 minutes and the order will be counterbalanced.
13. Be reminded to engage in tobacco abstinence (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) and combustible marijuana abstinence for 10 hours in preparation for Laboratory Visit 2.
14. Tentatively schedule next study visit with a member of the research team.

7.2.3 Laboratory Visit 2

During Laboratory Visit 2, (Duration: ~ 2 hours) participants will:

1. Arrive at the Center at approximately 1:00 PM after having abstained from tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) and combustible marijuana for 10 hours prior to visit.
2. Provide a carbon monoxide (CO) breath sample: abstinence verified by a CO measurement of < 10 ppm or < 50% of Visit 1's CO value
3. Provide a 30ml (2 tablespoons) urine sample to conduct cotinine analysis: abstinence verified by a cotinine reading < Visit 1's cotinine value; participants already measuring in the lowest tier are expected to remain there
4. Complete concomitant medication review

5. Complete forms re: use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month
6. Complete Adverse Events Form (Open-Ended AEs)
7. Be introduced to and briefly practice the Relative Reinforcing Value of Flavoring (RRVF) computerized lab task.
8. Complete computerized lab task: Relative Reinforcing Value of Flavoring (RRVF).
9. Use study-provided cigarillos during a session in our smoking lab (required). Following the RRVF task, participants will take earned cigarillo puffs, then complete a standardized one-hour wait period in the laboratory.
10. Be reminded to engage in tobacco abstinence (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) for 10 hours in preparation for Laboratory Visit 3.
11. Tentatively schedule next study visit with a member of the research team.

7.2.4 Laboratory Visit 3

During Laboratory Visit 3, (Duration: ~ 2.5 hours) participants will:

1. Arrive at the Center at approximately 1:00 PM after having abstained from tobacco (e.g., combustible cigarettes, e-cigarettes, cigars, blunts) and combustible marijuana for 10 hours prior to visit
2. Provide a carbon monoxide (CO) breath sample: abstinence verified by a CO measurement of < 10 ppm or < 50% of Visit 1's CO value
3. Provide a 30ml (2 tablespoons) urine sample to be used for urine cotinine analysis: abstinence verified by a cotinine reading < Visit 1's cotinine value; participants already measuring in the lowest tier are expected to remain there
4. Complete concomitant medication review
5. Complete forms re: use of marijuana, other tobacco products (besides cigarettes), or vaping of any substance including tobacco/nicotine or other drugs in the past month
6. Complete Adverse Events Form (Open-Ended AEs)
7. Begin a 90 minute cigarillo smoking ad libitum session, followed by a 30 minute period of no smoking. During this portion of the visit, the participant will be required to use study-provided cigarillos during a session in our smoking lab.
8. Be provided with resources on tobacco cessation services. Participants will also review an educational and prevention materials that explain the study rationale and the importance of cigarillo cessation, and the role that flavoring may play in future cigarillo use.

7.3 Table 1. Study Measures and Time Points

Table 1. Measures	Bio-behavioral Laboratory Visits		
Description of Time Point	**Visit 1**	**Visit 2**	**Visit 3**
Demographic & Baseline Covariates			
Demographics	X		
Tobacco History	X		
Nicotine Dependence	X		
CO	X	X	X
Urine Cotinine	X	X	X
Predictor Variables			
Risk Perceptions	X		
Sensation Seeking	X		
Depression	X		
Cigarillo Advertising & Marketing Exposure	X		
Marijuana & Alcohol use	X	X	X
Tobacco use	X	X	X
Outcome Variables			
Subjective rewarding value of cigarillo flavoring	X		
Relative reinforcing value of cigarillo flavoring		X	
Absolute reinforcing value of cigarillo flavoring			X

7.4 Description of Study Measures

7.4.1 Screening

Urine Drug Screen: A urine sample (~30ml) will be collected at Laboratory Visit 1 to conduct a urine drug screen. The urine drug screen indicates whether the subject has recently taken any of the following recreational drugs or medications: THC, cocaine, opiates, amphetamines, methamphetamines, phencyclidine (PCP), ecstasy (MDMA), barbiturates, benzodiazepines, methadone, tricyclic antidepressants, and/or oxycodone. Participants with a positive urine drug screen for any substance listed above other than THC and (prescribed) amphetamines and/or tricyclic antidepressants will be deemed ineligible. A urine sample that doesn't register a temperature reading of at least 90 degrees Fahrenheit will not be considered a valid sample. In an effort to remain CLIA-compliant, results from urine drug screen will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results. In order to document inclusion/exclusion criteria for regulatory purposes, results of the urine drug screens (test cup) will be retained in research charts and in an electronic research record within our local data management system (Access). These results are not and will not be entered into a participant's electronic medical record.

Urine Pregnancy Test: At Laboratory Visit 1, female participants will be supplied with a simple, CLIA-waived hCG pregnancy test strip and a urine sample cup. Female participants will be informed that pregnant women are not advised to participate in this research study. Participants will then be instructed to self-administer the pregnancy test and inform the study staff if they would like to continue participation after they have reviewed the results of the pregnancy test. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still receive travel reimbursement for the visit.

Breath Alcohol Concentration (BrAC): Participants will complete a BrAC assessment at Laboratory Visit 1. Participants will be made aware of the BrAC assessment prior to the visit and asked to avoid alcohol and alcohol-based products (e.g. mouthwash, breath spray, etc.) the evening and morning before Laboratory Visit 1. The BrAC monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading greater than 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than 0.000 at Laboratory Visit 1 will be deemed ineligible.

Medical History Form: A medical history form (led by the research staff) will be completed to review for applicable contraindications previously listed under Key Inclusion/Exclusion Criteria at Laboratory Visit 1.

Demographics and Smoking History: Standard surveys will collect demographics information such as age, sex, race, ethnicity, education level, and income. Standard survey questions will assess cigarillo use history (number and flavored), use of other combustible products, as well as cigarette smoking history (e.g., age at initiation, current smoking rate). Nicotine dependence will be assessed with the Fagerstrom Test for Nicotine Dependence (FTND). This 6-item measure has good internal consistency ($\alpha = .64$) and high test-retest reliability. Nicotine dependence will also be assessed using the Hooked on Nicotine Checklist (HONC).

Adverse Events Form (Open-Ended AEs): Participants will be asked an open-ended question about any symptom or medical event that may be related to their study participation. These events will documented as **unanticipated (unexpected)** AEs unless they are otherwise outlined in the protocol and/or consent form (i.e. related to withdrawal, assessments, etc.). The reporting period for each assessment will inquire about any event(s) or symptom(s) experienced since the last in-person visit. If a participant reports a symptom or medical event, they will be asked to rate the severity of the

event utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Issue does not interfere with usual daily activities), 2 (Moderate=Issue does interfere with some activities), and 3 (Severe=No normal activities are possible). See section 8.2.1: AE Collection Methods for further details.

Carbon Monoxide (CO) will be measured using a Vitalograph CO monitor (Lenexa, KS). A CO > 5 is indicative of combustible cigarette smoking. At the start of visits 2 and 3, 10-hour tobacco abstinence will be assessed via CO < 10 or 50% of the CO value measured at Visit 1.

Urine Cotinine will be measured using a test strip kit that detects the presence of cotinine in a urine sample along three detection levels: low, medium, and high. The testing kit indicates the presence and amount of cotinine measured in the urine, which is a product of nicotine metabolism with sensitivities of 50 ng/mL (low concentration), 200 ng/mL (medium concentration), and 600 ng/mL (high concentration). Participants will provide a urine sample for cotinine analysis with the expectation that cotinine level will be at least one tier lower than cotinine level at Visit 1; participants already measuring in the lowest tier are expected to remain there.

Concomitant Medications: At Laboratory Visit 1, participants will be asked to list all medications (prescription or non-prescription) and NRTs currently taken and/or recently discontinued (within the past 14 days) as a baseline collection. All information will be collected on a Concomitant Medication Log that will be maintained within the participant's study chart. At every subsequent in-person visit, participants will be asked if they have taken any additional medications (prescription or non-prescription), NRTs, and/or changed the dosage or stopped taking any previously reported medications since their last in-person visit. Participants who report taking contraindicated medication(s) over the course of the study period may only remain eligible if the Principal Investigator determine that the contraindicated medication(s) did not impact the study design, data quality, and/or participant safety and welfare.

7.4.2 Covariates – All Measured at Laboratory Visit 1

Demographics. Sex, age, education and employment will be measured at baseline. Available research suggests that women are more likely than men to use flavored cigarillos [8]. Cigarillo use history (number, flavor preference) will be included in the statistical models.

Risk perceptions of flavored cigarillo use (e.g., impact of flavor on risk and addictiveness) will be measured with six Likert-style items derived from previous and ongoing research (0=not at all to 6=extremely). The Center for Epidemiologic Studies **Depression** Scale (CES-D) is a 20-item Likert- style measure with high internal consistency (α >.85), and correlates with clinical ratings of depression severity. The CES-D has been used in adolescent and young adult tobacco studies. Young adults who use cigars such as cigarillos report higher levels of depression symptoms compared to those who do not use cigarillos. Flavoring appears to enhance the mood of young adults who use cigarillos. As such, we will not screen out for elevated depression symptoms. We will measure them and include them as a covariate in the statistical models as depression symptoms may underlie flavor preference. **Sensation seeking** will be measured with the 8-item Brief Sensation Seeking Scale (1=strongly disagree to 5=strongly agree) given its associations with little cigar and cigarillo use [47,100,150,151]. **Exposure to flavor-related advertising and marketing practices** will be measured with 9 items adapted from PATH and previous research. These items evaluate the source (e.g., Internet, social media, retail stores) and type (e.g., giveaways, direct mail and e-mail coupons, links to on-line vendors, branded merchandise, celebrity endorsement, music event sponsorship) of exposure to flavored cigarillo promotions.

Standard epidemiological items will measure lifetime and current use (monthly, weekly, daily, and rate) of **other tobacco products** such as combustible cigarettes (including menthol status), e-cigarettes, large and little cigars, and hookah. Lifetime and current use of **marijuana** (combustible, vaporized, and edible) will be assessed via items used in previous research and surveillance studies. Use of cigarillos for blunts will be measured and differentiated from cigarillo tobacco use

as intended. **Alcohol use** will be measured with epidemiological questions of lifetime, past 30 day use, as well as binge drinking episodes.

7.4.3 Outcome variables

Subjective rewarding value of cigarillo flavoring will be measured with the Cigarette Evaluation Scale (CES) adapted for cigarillo use. The CES is an 11 item Likert-format (1=not at all to 7=extremely) self-report instrument with established validity and reliability ($\alpha > .80$). We will focus on the satisfaction subscale. Primary Outcome measured at visit 1.

Relative reinforcing value of cigarillo flavoring will be measured with a validated choice paradigm, evaluating the preference for sweet flavored vs non-flavored cigarillos. RRVF will be defined by the breakpoint (highest trial completed across 10 trials to earn puffs for sweet flavored versus non-flavored cigarillos) Primary Outcome measured at visit 2.

Absolute reinforcing value of cigarillo flavoring is operationalized as the number of sweet flavored versus non- flavored cigarillo puffs consumed during the ad libitum smoking session. A research assistant will videotape, monitor, and count the number of cigarillo puffs taken during the 90-minute period. The primary comparison is the amount of consumption (puffs) of the sweet flavored versus non-flavored cigarillo. Primary Outcome measured at visit 3.

7.5 Analytic Plan

Prior to analyses, standard data cleaning, assumption evaluation, and imputation methodology will be applied. We conservatively assume that 85% of our participants will complete all study visits, and will recruit additional subjects (15%, 13) to replace those who fail to return. The baseline characteristics of subjects who drop out will be examined, with attention to whether there is an association between dropout and flavor preference. Female sex and race will be included in each model. We will also consider baseline variables potentially important to flavor preference (e.g., cigarette smoking status, menthol brand, cigarillo history, prior flavor preference, blunt use, depression, sensation-seeking, cigarillo flavor risk beliefs, and exposure to cigarillo flavor marketing) for inclusion in the multivariate models if bivariate associations with the outcome are $p \leq .20$. Outcomes will be analyzed using general linear models (GLM) with outcome family and links appropriate to each of the respective measures. Where measures are repeated, GLMs will be fitted with generalized estimating equations (GEE).

Aim 1 H1 will determine whether the subjective rewarding value of a sweet flavored cigarillo is greater than that of a non-flavored cigarillo among young adults. H1 will test whether participants report greater subjective rewarding value from a sweet flavored cigarillo than a non-flavored cigarillo. The outcome measure used for analysis is a continuous subjective rating of reward for sweet flavored and non-flavored cigarillos obtained at the first exposure (visit 1). The analysis will use a paired t-test (or GLM equivalent) to assess the effect of flavor. Female sex and race will be included in the model.

Aim 1 H2 will determine whether the relative reinforcing value of a sweet flavored cigarillo is greater than that of a non-flavored cigarillo among young adults. H2 will test whether participants "work harder" for sweet flavored cigarillo puffs than non-flavored cigarillo puffs (i.e., higher relative reinforcing value) as measured by a choice task. Participants will be given the choice to "work for" sweet flavored puffs at an increasing behavioral cost (more mouse clicks) or non-flavored puffs at a low fixed cost. The outcome variable used for this analysis is a breakpoint representing the highest level of work a participant will perform for a puff of a sweet flavored cigarillo. Flavor is inherent in the breakpoint outcome and will be assessed using a GLM.

Aim 1 H3 will determine whether the absolute reinforcing value of a sweet flavored cigarillo is greater than that of a non-flavored cigarillo among young adults. H3 will test whether participants take more puffs from a sweet flavored cigarillo versus a non-flavored cigarillo during the ad-libitum smoking session. The outcome measure is puff counts of sweet flavored and non-flavored cigarillos, and preference will be estimated as a rate-ratio using negative binomial mixed models.

Sample Size / Power. The proposed study is a within-subjects design. The sample size is driven by the test for H3. Because we have three experimental outcomes, we will Bonferroni correct our global alpha of 5% for three tests. Informed by the effect size of our prior study investigating e-cigarette flavoring (Cohen's d of 0.5) with a small within-subjects correlation (negative binomial model) of r=0.13. A sample of 86 yields 80% power to detect an effect size of 0.5, testing at alpha = 0.017.

8 Risks / Benefits

8.1 Potential Study Risks

The potential risks to participants, their likelihood and seriousness, and strategies to mitigate risks are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions/AEs will be collected, assessed, and reported as per the study protocol (see section 8: Safety and Adverse Events), federal law, and University of Pennsylvania regulations.

Cigarillo Smoking: The study-provided cigarillos you will be asked to smoke are commercially available. During the course of this study, participants will smoke flavored and/or unflavored cigarillos. At Visit 1, participants will take 6 puffs of a cigarillo. At Visit 2, participants will take 10 puffs of a cigarillo. At Visit 3, the number of puffs participants take is up to them. Some participants may experience certain symptoms while taking puffs of cigarillos, like nausea, dizziness, and/or rapid heartbeat. These feelings are typically mild and relatively short-lived. These symptoms are more common among individuals who have not have prior exposure to tobacco products and thus have not had previous exposure to nicotine. The chances that participants will experience these symptoms are less likely because they have had prior nicotine exposure. The informed consent form states that, if participants do experience these symptoms, they may let a member of the research staff know immediately and will be permitted to extinguish their cigarillo, even if they are in the middle of a smoking task.

Withdrawal Symptoms: Participants may experience uncomfortable withdrawal symptoms during their 10-hour tobacco abstinence. In preparation for the 10-hour tobacco abstinence, participants will receive tips for remaining abstinent (e.g., coping with withdrawal and craving, smoking triggers, coping with stress). Participants will also be reminded that these symptoms will be short-lived and that they will receive incentives for participation.

Reproductive Risks: Smoking can cause serious harm to unborn children or children who are breast-feeding. Female participants are asked to use a medically accepted method of birth control (such as IUD, birth control pills, condoms, etc.) while participating in the study. Further, female participants, and those assigned as female at birth, will be asked to administer a simple, one-step hCG pregnancy test and informed that if they are (or believe they may be) pregnant that they will not be eligible to participate in the research study. If a female participant becomes pregnant over the course of the trial, they will be immediately withdrawn. It will also be recommended that the participant seek consult from an obstetrician or maternal-fetal specialist about the dangers of smoking while pregnant.

Assessments: Some participants may experience some emotional distress during the assessments due to learning their carbon monoxide levels or seeing how many cigarillos they smoke. These events happen very rarely and in almost all cases are short-lived and of low intensity. If a participant does exhibit a high level of emotional distress, however, they will be offered contact information for mental health services in the area.

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related participation via email. Email is not a secure means of communication. Email messages travel across the Internet passing through multiple computers before reaching their final destination. It is not possible to know whether an email a participant sends will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have an archive of everything that is sent. If someone gets access to an email account (for example, a participant's family member), they could see archived messages. There are many other ways in which emails are not secure—these are only selected examples. To manage this risk the informed consent form will include specific language to educate research participants on the privacy risks involved in email communications. Participants will also be explicitly instructed to only use email communications for routine matters and never for personal or confidential messages or questions.

Confidentiality and Loss of Privacy: See section 9.6.1 and 9.6.2 for methods in which Confidentiality and Subject Privacy/Protected Health Information will be secured and maintained.

8.2 Potential Study Benefits

Young adults may benefit from participation by knowing that they are contributing to research that can ultimately help protect young adults like themselves from becoming regular cigarillo smokers. The proposed study is expected to yield new knowledge regarding the subjective, objective, and behavioral impact of sweet flavoring on cigarillo use among young adults, while controlling for other variables that may also impact the use of sweet flavored cigarillos. The findings will inform public health interventions and regulatory actions to reduce cigarillo use in this vulnerable population. The benefits outweigh the minimal risks associated with participation.

8.3 Risk/Benefit Assessment

The potential benefits of this study outweigh the potential risks. There is only a minimal risk of experiencing study-related AEs or SAEs by enrolling in this trial. The findings from this study will inform public health interventions and regulatory actions regarding the appeal of flavoring in cigarillos.

8.3.1 Adequacy of Protection against Risks

Informed Consent. Informed consent/HIPPA forms will be signed electronically on REDCap or at Laboratory Visit 1 before any research activities are completed. Trained staff will provide a study overview, including the risk and benefits of being in the study. Staff will respond to all questions and inform potential participants that participation is voluntary. Preliminarily eligible adult smokers will be asked to provide informed consent for participation. After receiving informed consent, participants will provide a urine sample to assess drug use and/or pregnancy, which are exclusions for participation. Participants will receive a copy of their signed consent form.

Oversight and Monitoring. The Institutional Review Board at the University of Pennsylvania will monitor the protection of human subjects and the safe and secure collection and storage of data. This committee will assess the study before initiation and then annually at the time of Continuing Review. The IRB will ensure the scientific, technical, and statistical soundness of the research and guarantee that methods for the ethical and safe treatment of human subjects are in place.

Participant Safety. Eligibility criteria for this study will exclude any individual who would be at risk of adverse effects from participation in this study. Participant safety begins with the PI's thorough training and ongoing supervision of the project staff and study procedures. Weekly meetings will ensure an understanding and adherence to the study goals and data collection and management procedures. Personnel training by the PI will be considered to be of the highest priority and will

be addressed prior to the start of the study and on an ongoing basis. Training will help ensure that all processes and procedures for data collection and management are correctly applied and utilized. Specifically, but not exclusively, this training will ensure that research personnel understand the study's goals and objectives, data collection process, confidentiality, participant safety, all case report forms (CRFs), the manual of procedures (MOP), database software and the data management system (DMS), and all applicable standard operating procedures (SOPs) to attest that the study is conducted in a proper manner. Training will span study recruitment approaches, screening, assessment, follow-up of rescheduled participants, data entry and storage, and tracking study incentives.

Data Management. The CIRNA Data Management Core will be responsible for the data management system, the operational facets of this study, quality assurance, and data storage.

Data Collection, Processing, and Management. All data collection, processing, and management procedures will be standardized in a detailed Manual of Procedures (MOP). Hard-copy surveys will serve as source documents. All data are entered into a database located upon the secure server with dedicated uninterrupted power at the CIRNA. All indicated data entry and processing operations will be performed using Data Management System (DMS) software. Study personnel will access the menu driven DMS software to perform specific operations. For example, the DMS functionality will include subject tracking, data entry, data validation, and query tracking, standard reports, and tracking of all major study milestones (e.g., assessment and visit disposition), and the counterbalanced sequence of the order of flavors on laboratory visit 1.

Quality and Data Safety Assurance Practices. The PI will conduct training to ensure that all processes and procedures for data collection and procedures for data collection, processing, and storage are correctly applied and utilized. Confidential participant information will be collected and entered into the database. When this information exists on paper (e.g., updated contact information, alternative contact information) it will always be filed under lock and key. Upon entry of this data into the database, an auto-study ID will be generated. The auto-study ID will then generate and be linked to a participant ID in a separate table. Thus, contact information will never exist in the same DMS table as a participant ID. No one can gain access to an individual database unless they have been explicitly granted a user ID and password. The Center's database server and individual study databases have never been compromised as a result of the extremely rigorous and secure network firewall technologies. The secure servers are located in a specially designed, highly secured facility with dedicated uninterrupted power supply. Access to this server facility is strictly limited.

Adverse Event Reporting. In accordance with NIH and IRB guidelines, this protocol will employ the following mechanisms for adverse event reporting: (1) alert the IRB of any and all reports of serious adverse events; (2) inform all members of the study team of any and all reports of serious adverse events; (3) notify the NIH of any actions taken by IRB with regard to data safety monitoring.

9 Safety and Adverse Events

9.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others:
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event:
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study (regardless if study-related). Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A ***serious adverse event*** (SAE) is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period:
The study period during which AEs/SAEs will be reported is from the initiation of any study procedures until the end of the study. Any event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in the study after the final time point will be assessed and reported as appropriate.

Preexisting Condition:
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Post-study Adverse Event:
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization or Surgery:
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.2 Collection and Recording of Adverse Events

9.2.1 AE Collection Methods

All AEs and SAEs occurring during the study period will be captured through the methods described below:

1. Open-Ended AE Form: Participants will be asked an open-ended question about any symptom or medical event that may be related to their study participation. These events will be documented as **unanticipated (unexpected)** AEs unless they are otherwise outlined in the protocol or consent (i.e. related to withdrawal, assessments, etc.). The reporting period for each assessment will inquire about any event(s) or symptom(s) experienced since the last in-person visit. If a participant reports a symptom or medical event, they will be asked to rate the severity of the event utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Issue does not interfere with usual daily activities), 2 (Moderate=Issue does interfere with some activities), and 3 (Severe=No normal activities are possible). Any report on the Open-Ended AE Form will require additional follow up per the AE documentation and internal reporting procedures outlined below in section 8.2.2.
2. Spontaneous Assessment: Once enrolled, participants will be instructed to inform the research team about any notable symptom or medical event/concern throughout their participation in the study. A participant may also request the Principal Investigator be consulted about any reported medical event or concern of any severity at any time throughout their participation.
3. An “AE Note” template will be available to the research staff to collect supporting AE information and will function as the source document. However, research staff may collect AE information on any source document available to them and transfer the relevant information to a formal AE Note at a later time. Any notable AE reported spontaneously will require additional follow up per the AE documentation and internal reporting procedures outlined below in section 8.2.2.

9.2.2 AE/SAE Documentation and Internal Reporting Procedures

AE/SAE Documentation: At a minimum, follow-up information will include AE/SAE onset/resolution, description of event/course, severity, action taken, outcome, and possible relation to study participation.

Information surrounding AEs and SAEs will be initially recorded on the appropriate source document such as the SEC Form, an "AE Note" or SAE Form, and/or any document in which the AE/SAE information was originally recorded. All applicable AEs and SAEs will then be documented on a cumulative AE and SAE log maintained within the regulatory binder.

Completed documentation of applicable AEs will include the following information:

- Protocol Title and IRB#
- Subject Identifier
- Event Title
- Date Site Notified
- Event Start Date and Time
- Event Stop Date and Time
- Description of Event/Course (including sequelae)
- Severity:
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Expectedness per protocol and/or consent
    - Expected/Anticipated
    - Unexpected/Unanticipated
- Action(s) taken (if appropriate)
- Outcome (if appropriate)

Documentation of SAEs will include the following information on a standardized SAE Form:

- Protocol name and number
- Subject identifiers
- Demographic data
- Date Site Notified
- Date and time of SAE onset
- Date and time of SAE resolution, if available
- Course/Description of Event (including sequelae)
- Action Taken
- Outcome
- Follow-up plan

- Serious Status (What makes the event an SAE)
- Severity of the event
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Clinical assessment of subject conducted at time of SAE (if appropriate)
- Results of any laboratory tests and/or diagnostic procedures (if appropriate)
- Autopsy findings (if appropriate)
- Concomitant medications and therapies (excluding treatment of event)
- Relevant Medical History (if appropriate)

Internal Reporting Procedures: All relevant follow-up information outlined above (see AE/SAE documentation) concerning applicable AEs, including all information regarding the occurrence of previously reported event(s), will be reported to the Study Coordinator (or other senior personnel) and Principal Investigator to determine a course of action (e.g. continue to monitor), relatedness (causality) to the study, and expectedness (if not already established). This consult will be documented via email. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not (or unlikely) to be the cause.

SAEs that are still ongoing at the end of the study period must be followed up to determine the final outcome unless it has been determined that the study treatment or participation is not the cause. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately per this protocol.

9.3 Reporting of Serious Adverse Events and Unanticipated Problems

The reporting requirements of applicable SAEs and/or Unanticipated Problems including reportable AEs (see section 8.1 for definitions) to external entities are detailed in the following sub-sections:

9.3.1 Investigator reporting: notifying NIDA and FDA

The following events/reports will be submitted to the FDA and NIDA Project/Program Officer in a narrative format or on FDA Form 3500A:

- Unexpected fatal or life-threatening suspected adverse reactions (in relation to study-provided cigarillos) will be reported as soon as possible, but in no case later than 7 calendar days after the initial receipt of the information.

9.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB.

The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any AE (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the Principal Investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (According to the Penn IRB standard operating procedures [SOPs], an event is "related to the research procedures" if the event is deemed **probably or definitely related** to the procedures.")

Reporting Process:
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths (more rapid reporting requirements):
Deaths that occur during the course of a research study and that are:

- Unexpected; AND
- Related to the research study; AND
- When other participants are believed to be at an increased risk of harm

Must be reported to the IRB within 3 days from the time the investigator becomes aware of the death.

9.4 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of AEs/SAEs as noted above, as well as adherence to the study data and safety monitoring plan outlined in sections 8 and 10.

10 Data Management

The CIRNA Data Management Team has developed a data management system (DMS) that will facilitate the operational facets of this study, including determination of entry eligibility, production of lists of subjects for telephone contacts for scheduling, and data entry. The DMS uses the relational database product Microsoft Access as the primary software platform for data entry and validation, storage, retrieval, modification, and security. The DMS ensures data integrity through range and validity checks during the data entry process. Daily backups are performed to protect data against accidental destruction or corruption.

10.1 Data Management System Development

The CIRNA Data Manager will work closely with the trial investigators to develop an understanding of the data collection, storage, and quality assessment needs for the trial. This includes the design and development of the trial data collection forms and any additional administrative CRFs, to ensure that standardized, uniform data collection and data management procedures are implemented and sustained throughout the trial. The data collection forms will serve as templates for designing the data entry screens. The Data Manager will work closely with trial investigators and senior personnel to design, develop, and test an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents are incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

Prior to deployment and use by the research staff, the database and DMS will be subjected to extensive functional testing. This testing is conducted according to a written test plan and is intended to verify the proper functioning of all components of the DMS. Any components that do not function as they were intended will be identified and evaluated by the development team to determine appropriate corrective action. Testing will also include an evaluation by user representatives for adherence to the requirements established by the intended users for the DMS. Successful completion of these user acceptance tests will mark the end of development and predicate the deployment of the DMS for use in storing and managing active trial data. Any modifications made to the DMS will be conducted in accordance with change control procedures.

10.2 Data Security

All research data for the trial will be stored in an electronic Access database that is managed by the Data Manger. The database will be hosted on a secure computing server and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. The Data Manager will maintain the database in an appropriate manner for the retention period required by regulation. Database administration includes user account maintenance, database security, performance monitoring, and database change management.

10.3 Data Processing

The data entry screens will resemble the data collection forms as closely as possible to allow visual referencing during data entry. This data entry module will be configured for single data entry. Participant data will be collected by research staff, recorded on study-specific CRFs, and scanned in or entered directly into the appropriate DMS module. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and/or skip pattern enforcement. Following telephone eligibility screening, research staff will perform subject registration. Following Laboratory Visit 1, research staff will randomize eligible subjects. The randomization module will allow the research staff to randomize subjects into one of the two trial arms. At the randomization attempt, the DMS will check the eligibility data to confirm that randomization is valid. A randomization assignment will then be provided.

10.4 *Data Quality Assurance*

A data quality module will be developed to assess data entered into the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will

be defined by the data manager, working closely with trial investigators, to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. The research staff will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data items will be managed by the research staff. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

Monitoring of trial progress will be accomplished, in part, through the use of standard reports. The Data Manager will program a set of standard enrollment, tracking, quality review, and safety monitoring reports. Data audits will occur after the first few participants are enrolled and periodically during the trial to detect errors in data entry. Eligible participants will have 100% of their source document information compared with the data entered in the database. Any errors will be investigated, resolved, and a plan will be implemented to prevent further errors should concerning patterns emerge.

10.5 Subject and Specimen Tracking

The Data Manager will develop a module to assist research staff in recruitment and retention tracking for trial subjects. This module will accept and store contact information for potential subjects and will include data items to indicate the completion status of significant events. The tracking module will include information about contact and visit schedules to assist in preparing communications to potential subjects and trial participants concerning scheduled events. The module will also allow for incentive-related inventory management. When obtaining saliva specimens, the research staff will complete a specimen registration CRF and scan/enter the data into the DMS. A unique specimen identifier will be assigned and recorded on the CRF. Labeled specimens and applicable information will be transferred to the lab for analysis as required for analysis.

10.6 Data Handling and Record Keeping

10.6.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI. Note in the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Confidentially of study data will be maintained in the following manner:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
- Prior to access to any study-related information, personnel will be required to review and sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.
- Precautions are in place to ensure the data is secure by using passwords and encryption.

Since self-report data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the data management system has set up several safeguards to prevent unauthorized access to participant data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying subject information is directly linked to bio-samples or results. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All subject data that can be linked to the study ID will be stored in the secure data management system, which has limited, password-required access. The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 10.6.2 below.

10.6.2 Subject Privacy/Protected Health Information

The following protected health information (PHI) may be collected as part of this study:

1. Name
2. Street address, city, county, zip code
3. All elements of dates (except year) for dates directly related to an individual and all ages over 89
4. Date of birth
5. Social Security Number
6. Telephone number, email address
7. Any other unique identifying number, characteristic, or code
8. Results from all questionnaires, tests, and procedures

Potential participants will be contacted over the phone after responding to recruitment efforts or having agreed to be contacted for future studies. Only individuals who have responded to recruitment efforts or who have agreed to be contacted regarding research studies at our Center will be contacted. If an individual cannot be reached immediately, staff members will identify themselves only as calling from the University of Pennsylvania; no mention will be made of the inquiry regarding study participation. Participants will undergo an initial telephone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they be asked to attend an in-person visit to confirm eligibility. All data collected over the phone and during in-person visits will be collected by research staff that have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Once enrolled, information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. All analyses will be conducted on de-identified data.

Data will be accessible only to the Study Investigators, study staff, applicable Center staff, UPenn IRB, Office of Clinical Research, authorized UPENN staff (e.g. accounting and billing matters, provide treatment, etc.), National Cancer Institute, and the FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify subjects. At most, the website will include a summary of the results. Subjects may search this website at any time.

11 Data and Safety Monitoring

11.1 Research Roles

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, research staff, and the IRB. The research staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms (CRFs), ensuring all fields are completed appropriately, and all error corrections are done according to GCPs. Any inconsistencies/deviations will be documented and addressed as appropriate. The research staff will perform regular chart reviews to verify data integrity. The Study Coordinator (or senior personnel) and Principal Investigator will maintain the study regulatory binder/essential documents per GCP. Research staff will meet and communicate on a regular basis to reconcile data queries and safety concerns. The IRB will review the trial on an on-going basis per institutional and federal regulations until the study is formally closed-out.

11.2 Staff Training

Staff training will consist of an initial explanation and review of the protocol, informed consent form, CRFs and laboratory tasks, sample collection protocols, data management system, adverse event collection and reporting, and all study-specific SOPs. In addition, during a standardized training period, the duties of each staff member will be clearly outlined and all applicable regulations will be reviewed. Training interactions will be documented in a training log, which will be maintained within the regulatory binder. Senior personnel will supervise junior staff and provide re-training as needed.

All personnel working on this project will complete required training in the protection of human subjects and the protection of personal identifiable information (i.e. HIPAA) before interacting with study data or research participants. All human subject and privacy protections certifications will be maintained in the regulatory binder.

11.3 Monitoring Activities

11.3.1 AE/SAE Monitoring

Monitoring and management of AEs/SAEs will be conducted in real-time by the Principal Investigator and the research team at regular time points as per the methods and procedures detailed in section 8: Safety and Adverse Events.

11.3.2 Initial Assessment Monitoring

The study staff will conduct a manual review of source documents and CRFs for all subjects determined to be eligible at telephone screen and again prior to Laboratory Visit 1. Eligibility data will be reviewed in real-time at Laboratory Visit 1 by the research staff. In addition, The Study Coordinator (or senior personnel) will verify that all data have been collected and, when applicable, meet the eligibility criteria on a “Final Eligibility Checklist.” The Final Eligibility Checklist will be signed and dated by the Study Coordinator (or senior personnel) to formally document review. In addition to confirming eligibility, a brief, internal report describing the findings will be compiled and distributed to study staff (if applicable). If the Study Coordinator (or senior personnel) notes a pattern of improper data collection or deviations, additional trainings will occur.

11.3.3 Protocol Monitoring

Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as identifying, reporting, and rectifying protocols deviations, reviewing for violations of inclusion/exclusion criteria, and ensuring the adherence to study-specific SOPs, GCP, and other federal and institutional regulations. Protocol monitoring will be performed on an ongoing basis through the following methods:

1. Checklists will be utilized at all time points to ensure all data is collected per protocol and procedures are followed as appropriate.
2. A Final Eligibility Checklist will be completed after Laboratory Visit 1 for all participants who enroll (i.e. sign consent) in the study. The Final Eligibility Checklist will serve as final confirmation of eligibility status.
3. A complete chart review of a randomly selected participant charts. The chart review procedure is a thorough review of all source documentation to ensure the integrity of the data, all study paperwork is present, all fields are completed per GCP, and all study-specific SOPs have been followed appropriately.

11.3.4 **Database Auditing**

As outlined in Section 10: Data Management, the study DMS will be equipped with internal validation checks to ensure data is entered within reasonable ranges. Error messages will be displayed in real-time if data appears inaccurate. Staff will have to respond to these error messages before data can be saved. In addition, The Study Coordinator (or senior personnel) will perform regular milestone quality assurance checks.

11.3.5 Data Security

As outlined in section 10: Data Management, study data will be secured through controlled user access and accessible to authorized personnel only. Source documents will be secured in locked filing cabinets.

11.4 Frequency of Data and Safety Monitoring

Data will be reviewed internally on a regular basis. Specifically:

1. At data capture, the research staff will review data for completeness and integrity.
2. At data entry, the DMS will include multiple internal validity checks which will prompt the staff if an entry was made that is out of range or in an unacceptable format.
3. Eligibility data will be reviewed in real-time at Laboratory Visit 1. In addition, the Study Coordinator (or senior personnel) will review and verify that all data have been collected and, when applicable, meets the eligibility criteria on a “Final Eligibility Checklist.”
4. On a regular basis, the project staff will review data through an internal chart review procedure supported by the DMS. A random subset of eligible participants will be reviewed.
5. All CRFs for eligible subjects are 100% source-data verified through an internal data management system (Data Entry/Quality Assurance) on an ongoing basis.
6. The study statistician will review data prior to analysis to ensure integrity and validity.

11.5 Auditing and Inspecting

The Principal Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

12.1 Informed Consent

A fully trained staff member will obtain informed consent using the combined consent and HIPAA form approved by the IRB (UPENN). The consent process will take place prior to the initiation of any study procedures. The consent process will occur electronically via REDCap OR in person at the CIRNA and will involve a discussion of the study requirements and procedures. During in-person consent, the combined consent and HIPAA form will be read verbatim to participants. During electronic consent, the combined consent and HIPAA form will be completed virtually via REDCap. Participants will be required to read the entire consent in order to participate in the research study. Participants will have an opportunity to ask any questions and/or express concerns. Participants can elect not to participate and may withdraw at any time without penalty. Participants will receive a copy of the combined consent and HIPAA form for their records. In addition, participants will be given the Principal Investigator's contact information (located on pg.1 of the consent) should they wish to speak to the Investigator during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all participants will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for). The consent form must be signed and dated by the participant and the investigator-designated research professional obtaining the consent. The original signed combined consent and HIPAA form will be centrally stored in regulatory binders (consent).

13 RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

13.1 Research Staff

The following research staff will be directly involved with the implementation and execution of the current study:

- Janet Audrain-McGovern, Ph.D., Principal Investigator
- E. Paul Wileyto, Biostatistician
- Divya Manikandan, Research Staff
- Olivia Klapec, Research Staff
- Fodie Koita, Research Staff
- Susan Ware, Database Developer/Manager
- Joseph Smith, Data Management Staff

13.2 Study Facilities

This project will be conducted at and through the CIRNA. The CIRNA has successfully conducted similar protocols and has well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include ventilated smoking rooms, a large and small conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities.

If participants require referral for psychological services, information about such programs at 3535 Market Street and/or the Philadelphia area will be provided; we have a form with specific information about such programs already in use in other CIRNA studies.

14 Study Finances

14.1 Funding Source

This study is financed through a grant from the U.S. National Institute on Drug Abuse.

14.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14.3 Subject Compensation

Participants will be compensated for each in-person visit they attend and can receive up to $240.00 (including travel reimbursement) for successfully completing all of the study requirements in their entirety as per the Study Compensation table (Table 2) below.

All cases of non-compliance in regards to task and visit completion compensation will be reviewed on a case-by-case basis by senior personnel. A detailed compensation breakdown will be reviewed during the informed consent presentation and throughout the course of the trial.

Participants will be asked to complete a W-9 tax form (includes social security number) at the conclusion of Laboratory Visit 1 because the University of Pennsylvania is required to report to the Internal Revenue Service (IRS) any cumulative payments for participation in research studies at the University of Pennsylvania that exceed a total of $600.00 in a calendar year. A W-9 will aid the Center and University in tracking and reporting those who participate in multiple projects and accrue over $600.00 in a calendar year. Further, a social security number is required to register each participant for a Greenphire ClinCard (described below).

At the end of Laboratory Visit 1, eligible participants will be issued a Greenphire ClinCard, which is a reloadable, pre-paid card for the purposes of study compensation. Compensation will be loaded onto the ClinCard at the end of successfully completed visits. Participants may opt to receive a text message alert when a payment has been loaded onto the ClinCard.

14.3.1. Table 2. Study Compensation.

Visit	Visit Compensation	Travel Reimbursement	Total
Visit 1	$50.00	$5.00	$55.00
Visit 2	$60.00	$5.00	$65.00
Visit 3	$75.00	$5.00	$80.00
BONUS	$40.00 BONUS		
Total	$240.00		

15 References

See the NIDA grant proposal for references.