Consortium on Methods Evaluating Tobacco (COMET): Filter Ventilation and Product Standards

COMET2: PROJECT 1 – STUDY 2

Telehealth study assessing the removal of cigarette filter ventilation on smoking behavior and biomarkers

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Revision History

	Revision Summary	Protocol Version date	Consent Form Version Date	IRB Approval Date
1	Change from “roll you own” cigarettes to a manufactured cigarettes; brief in person or curbside visit	5/11/21	5/11/21	6/23/21
2	Addition of buccal cell collection and inhalation measures on a subset of subjects; minor grammar corrections	8/5/21	8/5/21	9/17/21
3	Changed number of randomized subjects to 162; Increased cigarette per day eligibility criteria from 30 to 35 cigarettes; added Tobacco Policy Support Questionnaire; minor corrections	12/08/22	7/12/22	

Table of Contents

Abbreviations

AE: **Adverse Events**: is an undesired harmful effect resulting from a medication or other intervention / study procedure.

ANOVA: **Analysis Of Variance**: is a collection of statistical models used to analyze the differences between group means and their associated procedures

BDI-II: **Beck Depression Inventory, 2nd Edition**: created by Aaron T. Beck, is a 21-question multiple-choice self-report inventory, widely used instruments for measuring the severity of depression.

BP: **Blood Pressure:** is the pressure exerted by circulating blood upon the walls of blood vessels and is one of the principal vital signs.

COMET: **Consortium on Models Evaluating Tobacco:** the acronym selected for this program project grant.

CES: **Cigarette Evaluation Scale:** a 12-item questionnaire that assesses the degree to which smokers experience the reinforcing effects of smoking.

COPD: **Chronic Obstructive Pulmonary Disease:** is a type of obstructive lung disease characterized by chronically poor airflow.

CVD: **Cardiovascular Disease:** (also called heart disease) is a class of diseases that involve the heart, the blood vessels (arteries, capillaries, and veins) or both.

DVT/PE: **Deep Vein Thrombosis / Pulmonary Embolism:** deep vein thrombosis is a blood clot in the deep veins of the leg. If the thrombus breaks off (embolizes) and flows towards the lungs, it can become a life-threatening pulmonary embolism (PE), a blood clot in the lungs.

FDA: **Food and Drug Administration:** is a federal agency responsible for protecting and promoting public health through the regulation and supervision of tobacco products and other products.

FSPTCA: **Family Smoking Prevention and Tobacco Control Act:** is a federal statute signed into law by President Barack Obama on June 22, 2009 that gives the Food and Drug Administration the power to regulate the tobacco industry.

FTND: **Fagerström Test for Nicotine Dependence:** is a 6-item standard instrument for assessing the intensity of physical addiction to nicotine and includes an evaluation of cigarette consumption, the compulsion to use, and dependence.

GAD: **Generalized Anxiety Disorder-7 item questionnaire assessing severity of anxiety symptoms.**

hCG: **Human Chorionic Gonadotropin:** is a hormone produced by the placenta following implantation. The presence of hCG is detected in pregnancy tests.

HIPAA: **Health Insurance Portability and Accountability Act:** A law designed to provide privacy standards to protect patients' medical records and other health information.

HR: **Heart Rate:** a measure of the number of heart beats per minute (bpm)

ITR: **Interactive Text Response:** Text messaging using Twilio, a service that invites participants via a web link unique to the participant for completion of a daily REDCap survey. REDCap stores all phone numbers and survey data. No data is ever saved by Twilio.

MNWS: **Minnesota Nicotine Withdrawal Scale:** An 8 item scale assessing symptoms of tobacco withdrawal.

NIAAA: **National Institute on Alcohol Abuse and Alcoholism:** part of the U.S. National Institutes of Health.

NCI: **National Cancer Institute:** part of the U.S. National Institutes of Health.

NIH: **National Institute of Health:** an agency of the United States Department of Health and Human Services.

NMR: **Nicotine Metabolite Ratio:** is a urinary measure of the ratio of nicotine metabolites, which indicates speed of nicotine metabolism.

NNAL: **4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol:** One of the tobacco specific nitrosamines, one of the most important groups of carcinogens in tobacco products, which are formed from nicotine during the curing and processing of tobacco.

OSU: **Ohio State University**

PATH: **Population Assessment of Tobacco and** H**ealth:** a national, longitudinal study looking at tobacco use and health.

PI: **Principal Investigator:** is the lead scientist for a particular well-defined research project, such as a laboratory study or clinical trial.

PHQ (PrimeMD)**: Patient Health Questionnaire** (Primary Care Evaluation of Mental Disorders**):** Patient Health Questionnaire (PHQ –Pfizer©), a multiple-choice self-report inventory that is used as a screening and diagnostic tool for mental health disorders of depression, anxiety, alcohol, eating, and somatoform.

QSU: **Questionnaire of Smoking Urges:** a 10 item questionnaire to self-report smoking urges and cravings.

REDCap: **Research Electronic Data Capture (web based software):** is a secure, HIPAA compliant, web-based application for building and managing online surveys and databases.

SAE: **Serious Adverse Event:** generally, any event which causes death, permanent damage, birth defects, or requires hospitalization is considered an SAE.

SGR: **Surgeon General's Report**

SIDS: **Sudden Infant Death Syndrome:** is the sudden unexplained death of an infant.

TLFB: **Timeline Follow-back:** is a method that can be used as a clinical and research tool to obtain a variety of quantitative estimates of marijuana, cigarette, and other nicotine products by asking clients to retrospectively estimate their usage prior to the interview date.

TNE: **Total Nicotine Equivalents:** a urinary measure of nicotine and its metabolite concentrations.

UMN: **University of Minnesota**

WISDM: **Wisconsin Inventory of Smoking Dependence Motives (Brief):** a 37 item questionnaire to measure tobacco dependence by measuring a variety of smoking motives.

Study Synopsis

Study Design:	This single-blind, between-subject, randomized, multi-center study will assess the effect of cigarettes with unventilated vs. ventilated filters on smoking behavior and biomarkers of tobacco toxicant exposure. The study uses telehealth and brief in-clinic or curbside visits and will also examine the feasibility of remote collection of multiple biological samples. Subjective measures, alveolar carbon monoxide, blood pressure and cigarettes per day will be collected remotely. Biological samples collected at home will be dropped off at the clinic during a brief clinic or curbside visit where the study cigarettes will be dispensed.
Primary Aim:	To examine the effects of unventilated vs ventilated filter cigarettes on urinary biomarkers of toxicant exposure and smoking behavior (e.g., cigarettes per day, intensity of smoking).
Secondary Aim	To examine the effect of unventilated vs. ventilated filter cigarettes on cigarette dependence and subjective responses to cigarettes (e.g., perceptions of harm).
Exploratory Aim	To examine how the biomarkers analysis collected via different biological samples are concordant.
Population:	Cigarette smokers
Study Procedures:	Smokers using conventional cigarette brands with filter ventilation of about 16-36% will enter a three phase study. Phase 1 is a 1-week baseline period of smoking usual brand cigarettes; Phase 2 consists of 2 weeks of smoking ventilated study cigarettes; and Phase 3 where subjects are randomly assigned to one of two conditions: 1) ventilated cigarettes; or 2) unventilated cigarettes smoked for a 6 week period. Weekly telehealth visits are conducted to collect study measures and subjects attend a brief clinic or curbside visit to pick up study cigarettes and drop off biomarker samples. A follow-up telehealth visit will occur at one-month post intervention.
Accrual Goal:	162 (81 per group) enrolled
Enrollment Period	May 2021 – December 2022

1 Study Objectives and Hypotheses

The goals of this project are to determine the effects of varying degrees of cigarette filter ventilation on biomarkers of toxicant exposure and smoking behavior and on subjective responses to the cigarette.

1.1 Primary Objective

The primary aim of this study is to examine the effects of ventilated vs. unventilated filter cigarettes on smoking behavior (cigs/day, smoking intensity) and biomarkers of toxicant exposure.

1.2 Secondary Objectives

The secondary objectives are to examine the effects of cigarette filter ventilation on subjective measures such as cigarette dependence and responses to study cigarettes. As an exploratory analysis, the concordance for toxicant levels analyzed across multiple biosamples (urine, saliva, blood spots and hair) and subject acceptability of collecting these samples at home will be determined.

We hypothesize that unventilated filter cigarettes will be associated with no higher number of cigarettes smoked, biomarkers of exposure or cigarette dependence and satisfaction compared to ventilated filter cigarettes; but smokers assigned to the ventilated filter cigarettes will smoke cigarettes more intensely and perceive them as less harmful than smokers assigned to the unventilated cigarettes. We also hypothesize the level of toxicant exposure will be concordant across various methods of collecting biological samples.

2 Background

The Changing Cigarette. Over 34 million people in the United States,[1] and about 1.2 billion globally,[2] smoke cigarettes. With about 500,000 deaths per year in the US[1,3] and 6 million per year worldwide,[2] it is critical to have strong tobacco control policies in place to minimize the casualties from tobacco use.

The Family Smoking Prevention and Tobacco Control Act (FSPTCA), signed into legislation in 2009, provides the FDA with the authority to regulate tobacco products. One of the provisions in this legislative act empowers the FDA to assert product standards that would reduce harmful constituents in tobacco products, including alterations in the design of the product. A product standard that requires consideration is the use of ventilation in cigarette filters. Filter ventilation came onto the marketplace in the 1960s in response to consumer concerns about the negative health impact of cigarettes after a series of reports, including the 1964 U.S. Surgeon General's Report[4] (SGR), linked smoking to lung cancer and other diseases. Filter ventilation was a way for the tobacco industry to reduce machine-determined tar and nicotine yields in cigarettes, providing consumers with the perception that these cigarettes were "safer" to smoke. This perception, however, was false because

smokers enhanced their puff topography (increased velocity, duration of puffs, puff volume, inhalation depth and reduced inter-puff intervals) and/or smoked more cigarettes per day to compensate for lower nicotine yields.[1,5,6] That is, filter ventilation made the cigarette more "elastic," allowing the smoker to manipulate the cigarette in ways to maintain the desired systemic level of nicotine. Research has shown that regardless of the extent of cigarette ventilation, among the range of ventilated cigarettes on the market, the amount of nicotine and other toxicant intake is similar when measured in the blood and urine, with the possible exception of the most highly ventilated cigarettes.[1,5-7] Furthermore, ventilated cigarettes provide the perception of smoothness that added to the consumers' false beliefs that these cigarettes are potentially healthier.[8,9] This misperception of less harm associated with smoking ventilated cigarettes, or what was marketed as "light" or "ultralight" cigarettes, led to the majority of smokers switching to or initiating smoking with ventilated cigarettes by the 1980s.[10] Unfortunately, not only did this cigarette design potentially reduce the number of people who would have otherwise quit smoking, but also it may have led to a higher incidence of adenocarcinoma lung cancer.

Filter ventilation and increased risk of adenocarcinoma. With decreasing smoking rates, the overall incidence of lung cancer in men declined over the last half century. However, while squamous cell cancers decreased, there was a paradoxical increase in the proportion of lung adenocarcinomas, counter to the expectations that all lung cancers would proportionately decrease. The risk for lung adenocarcinoma grew dramatically since the introduction of filter ventilation. Other methods were also used to reduce tar and nicotine yields (e.g., cut size of the reconstituted tobacco sheet, density of the tobacco in the rod, the composition and design of the filter material, the porosity of the cigarette paper, etc.), but they do not allow for elasticity of the cigarette. After reviewing these and other data, the 2014 SGR[1] concluded that, "adenocarcinoma has been increasing in the U.S. as a fraction of all lung cancers and becoming the most common histological type of lung cancer. Despite decreases in prevalence of smoking and smoking caused squamous cell carcinoma, the incidence of adenocarcinoma in smokers has increased since the 1950s when changes occurred in cigarette design and composition (p. 177)."

The 2014 SGR[1] further concluded that, "the evidence is not sufficient to specify which design changes are responsible for the increased risk of adenocarcinoma, but there is suggestive evidence that ventilated filters and increased level of tobacco specific nitrosamines have played a role (p. 186)." Since the SGR, after reviewing the scientific literature and tobacco industry documents, we have proposed in a weight of evidence review and causation analysis that there are several pathways and reasons by which ventilated cigarettes could increase adenocarcinoma lung cancer.[7] Ventilated cigarettes are associated with slower and lower temperature burn time leading to a longer time for the coal to smolder and less airflow, which results in the formation of more toxic combusted and incomplete combusted constituents and mutagens (e.g., 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanone [NNK], polycyclic aromatic hydrocarbons and volatile organic compounds) per mg of tar. Additionally, the slower burn time and increased resistance of the smoke allows for the particle to absorb more water and constituent gases. As greater volumes of smoke that contain higher amounts of harmful constituents are puffed and inhaled more deeply (due to compensatory smoking), they are more able to reach the distal regions of the lung where adenocarcinoma more commonly occurs. Furthermore, studies have shown that the peripheral parts of the lung contain greater amounts of cells that may be more sensitive to NNK and the development of adenocarcinomas.

It should be noted that filter ventilation is not considered to be the sole causative factor for higher incidence of adenocarcinoma lung cancer. An increase in levels of tobacco specific nitrosamines (TSNAs), such a NNK and N'-nitrosonornicotine (NNN), also occurred over the last half-century and so may be another important contributing factor. However, whether or not increasing NNK also contributed to the increasing adenocarcinoma does not preclude the FDA from regulating filter ventilation. It also should be noted that while the evidence for filter ventilation causing the adenocarcinomas is highly suggestive, there are reasons independent of this concern that would support regulating filter ventilation. These reasons include the misperceptions of relative health risks among smokers.

In our efforts to explore the effects of filter ventilation, our research group has recently conducted a cross-sectional analysis of a national survey showing that smokers of more highly ventilated cigarette demonstrated similar rather than higher levels of toxicant exposure as smokers of lower unventilated cigarettes; however smokers of more highly ventilated cigarettes reported lower levels of perceived harm of their cigarettes[11] which might contribute to the maintenance of smoking. To date, no study has systematically examined the effects of switching from ventilated to unventilated cigarettes on toxicity and appeal.

Developing the science to determine if filter ventilation should be banned. The 2014 SGR stated that, "if the risk of lung cancer has increased with changes in the design and composition of the cigarettes, then the potential exists to reverse the risk through changes in design and composition (p. 186)." The report went on to say that "even a modest reduction in the large burden of mortality from lung cancer would result in saving a substantial number of lives over time (p. 186)." This study will use a systematic and comprehensive effort to examine one type of design feature, based on extensive review of the literature that may have led to the increase in lung cancer deaths, in particular adenocarcinoma lung cancer. Independent of the effects of ventilated cigarettes on lung adenocarcinoma, removing filter ventilation has the potential to reduce misperceptions regarding the relative harm of these cigarettes. We begin with the premise that ventilated cigarettes should be regulated, and herein we study its complete removal. This proposed study complements other studies conducted by our research team examining the effects of cigarette ventilation levels on biomarkers from lung bronchoscopies and particle distribution in the lungs. The aim of this study will be to examine the impact of ventilated vs. unventilated cigarettes on several biomarkers of specific exposures and effects (assessed via urine, saliva, oral cells and potentially hair and blood and inhalation measures), and examining smoking topography via spent filter analysis while holding levels of TSNAs constant. The overarching goal is to make sure that a proposal to ban filter ventilation does not lead to greater toxicant exposure, dependence and thereby potential harm, complementing other program project studies that examine misperceptions of ventilated cigarettes and potentially greater harm by examining the effects of these cigarettes in the lung.

Note: The original NIH funded study design involved in person contact with the participants. This study was approved by the IRB (STUDY 00003531). Since the COVID-19 pandemic, we have limited our in-person contact while conducting human clinical trials that do not have a direct therapeutic benefit to the participant. Because it is unknown when we will be able to conduct the originally designed trial again and the uncertainty regarding the course of the pandemic, we have adapted this original study to be conducted primarily remotely, with a brief clinic or curbside component to drop off biosamples and pick up study cigarettes. The recent improvements in controlling the COVID-19 virus

has allowed us to conduct some of our measures face-to-face. As the situation continues to improve, we propose to resume the inhalation measures on a subset of study participants.

3 Summary

The **primary aim** of this study is to examine the effects of unventilated vs. ventilated filter cigarettes on an exposure biomarker of a potent lung carcinogen and smoking behaviors (e.g., cigarettes per day, filter analysis).

A **secondary aim** includes determining the effects of unventilated vs. ventilated filter cigarettes on cigarette dependence and subjective response to cigarettes.

Study Design

This is a randomized, single-blind, multi-site study where subjects (N=162; 81 in each group) are randomly assigned to one of two cigarettes with different filter designs: 1) Ventilated cigarettes; or 2) Unventilated cigarettes.

4 Subject Selection

4.1 Recruitment

Subjects will be recruited through various media (internet, television, newspaper, radio) or from a waitlist kept for those interested in potential studies. An example of the advertisement would read as follows:

Smokers are wanted for a [University of XX] study that provides cigarettes with different filters. It's free to participate and you may earn up to $855

4.2 Inclusion/Exclusion Criteria

Inclusion Criteria

a) Male or females at least 21 years of age.
b) Self-report of daily smoking of at least 5+ cigarettes and no more than 35 cigarettes for $\geq$3 months.
c) Biochemically confirmed regular smoking status (CO $\geq$8 ppm; if CO < 8 ppm, then nicotine level indicating regular smoking).
d) Smoking a current brand (or if smoking roll-your-own cigarettes, indicates a preferred manufactured brand) of 16-36% ventilation. This range of ventilation was chosen based on our pilot data (unpublished). A list will be provided with eligible brands that corresponds to the predominant type of cigarettes currently used by smokers, i.e., previously marked as "lights" and approximates the assigned ventilated study cigarettes.
e) Has regular access to a smartphone or tablet for use with CO device and smartphone, tablet or computer with functioning camera and internet access for telehealth visits and surveys.

Exclusion Criteria

a) Unstable health conditions (any significant serious, unstable medical condition including, but not limited to cardiovascular disease, liver or kidney disease, COPD, bronchitis within the past 3 months, seizure disorder and cancer (cancer-free ≤5 years except some skin cancers can be within 5 years), or as determined by the licensed medical professional at each site, a COVID-19 positive test or COVID-19 symptoms in the last 30 days).
b) Unstable mental health (to be determined by medical history, Patient Health Questionnaire (Prime-MD) after review by the licensed medical professional at each site.
c) Excessive drinking or problems with drinking or drugs-including marijuana (assessed by PI or licensed medical professional).
d) Use of other tobacco or nicotine products more than 9 days out of the last 30 days.
e) Currently pregnant, breastfeeding or intending to become pregnant for the duration of the study or unwilling to agree to use adequate protection to avoid pregnancy.
f) Taking exclusionary medications, unstable dosing of medications, or unstable control of symptoms for ongoing medical conditions (medications or conditions that would impact biomarkers or patient safety to be determined by the licensed medical professional at each site).
g) Vital signs outside of the following range:
    i. Systolic BP greater than or equal to 160
    ii. Diastolic BP greater than or equal to 100
    iii. Systolic BP below 90 and symptomatic (dizziness, extreme fatigue, difficulty thinking, inability to stand or walk, feeling faint)
    iv. Diastolic BP below 50 and symptomatic (dizziness, extreme fatigue, difficulty thinking, inability to stand or walk, feeling faint)
    v. Heart rate greater than or equal to 105 bpm
    Heart rate lower than 45 bpm and symptomatic (dizziness, extreme fatigue, difficulty thinking, inability to stand or walk, feeling faint). *Participants failing for heart rate or blood pressure will be allowed to re-screen once).*
h) Expired air carbon monoxide (CO) level greater than 80 ppm.
i) Household member enrolled in the study concurrently.
j) Participated in a prior research study during the past three months that would impact baseline smoking or response to study products.
k) Inability to independently read and comprehend the consent form and follow other written study instructions, materials or measures. Participants are required to complete parts of the protocol at home independently and must show ability to comply with directions.
l) Unstable living environment that would compromise the ability to sequester study products or complete study procedures.

Justification for Inclusion/Exclusion Criteria:

Individuals under age 21 are excluded because they cannot legally buy cigarettes. Requirement of 5+ cigarettes daily for the past three months ensures smoking stability. Those subjects considered to have unstable medical or medication conditions will be determined by site's medical professional and are excluded if these symptoms pose a safety issue or are believed to render the subject unable to fully participate in the study. Examples include but

are not limited to the following: angina, stroke, heart attack which occurred recently, blood clots in the arms or legs for which the individual is undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy, fractured limbs, severe arthritis, or other debilitating conditions of mobility, severe shortness of breath (caused by conditions such as uncontrolled asthma, COPD, or arrhythmia), active untreated infection such as pneumonia, active untreated endocrine disorder such as hyperthyroidism, COVID-19 or its symptoms, suicidal ideation or any other condition which is likely to impair the individual's ability to attend and fully participate in study visits and procedures. Pregnant and nursing women are excluded as cigarette use is detrimental to the fetus or infant. Current or recent (3 month) alcohol or drug abuse problems will be excluded as these factors could independently affect smoking behavior. Unstable living situations, such as homelessness, could compromise the subject's ability to control access to the study cigarettes and any medical or psychiatric conditions (to be determined by medical history and PHQ) that would be deemed to pose a safety issue to the subject.

4.3 Participant Registration

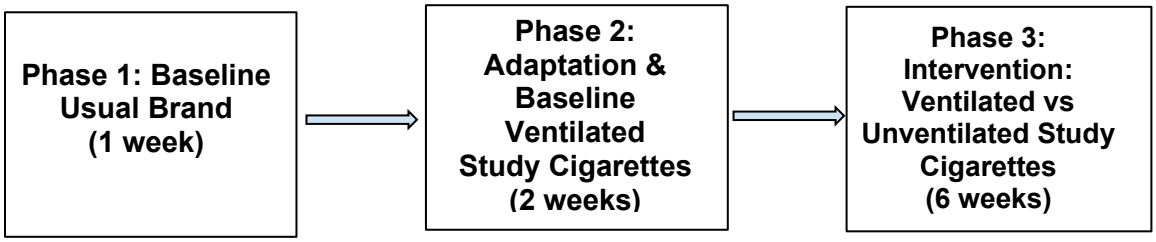
Study registration will occur after the informed consent process is completed, consent form is signed and screening eligibility is confirmed. No study procedures will be conducted until after the consent form is signed, either electronically or a paper copy mailed or faxed to the clinic. To be enrolled in this study following screening, the participant must meet each criterion listed on the eligibility checklist based on the eligibility assessment documented in the case report record. Upon completion of the screening evaluation, and confirmation of eligibility, the study coordinator or designee will enroll the subject into REDCap.

5 Experimental Design:

Smokers will undergo a screening and then a three phase, 9 week experimental trial (Figure 1) with a one month follow-up at Week 10:

1) Phase 1 – Usual Brand Baseline: 1 week baseline assessment period of usual brand cigarette smoking;
2) Phase 2 – Study Cigarette Adaptation & Baseline Period: 2 week period allows the subject to adjust to the ventilated study cigarettes and obtain baseline data prior to randomization;
3) Phase 3 – Intervention: Randomization to either ventilated or unventilated study cigarettes for 6 weeks.

Figure 1:

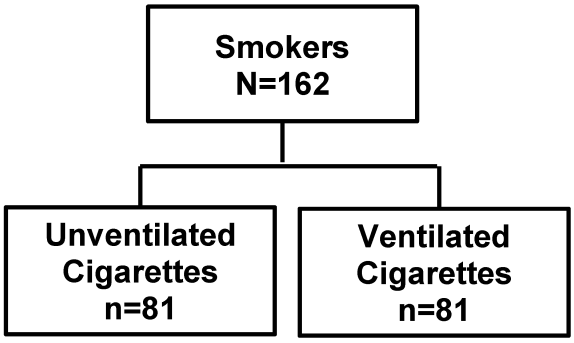


Design

Subjects will be randomized at the end of Phase 2 (Visit 00) to one of the two experimental conditions (ventilated vs. unventilated cigarettes) for the 6-week intervention. An intervention

of six weeks was chosen because compensation is likely to stabilize by two weeks and biomarker levels should stabilize by six weeks.[12,13]

Figure 2. Intervention Groups



Subjects will be informed of their assignment to ventilated cigarettes (cigarettes with similar ventilation as their usual brand) or unventilated cigarettes. As described above, study cigarettes are provided under single-blind conditions where subjects will not be informed of the filter design of the study cigarettes.

5.1 Investigational Tobacco Products

Tobacco Products:

Study Cigarettes: The study cigarettes will be a conventional manufactured cigarettes (e.g., Pyramid 100 mm). The investigational cigarettes are either: 1) ventilated (e.g., 28% +/- 4% filter ventilation); or 2) unventilated (e.g.,~0-5% filter ventilation). Product characteristics including blend of tobacco, additives, nicotine and tar content levels will be identical across these two cigarettes but will differ in the degree of ventilation (number of filter vents), e.g., no ventilation or ventilation (the extent of ventilation found in former “light” to “ultra-light” cigarettes). The dose of nicotine will be similar to usual brand cigarettes. The tobacco will be tested periodically to verify constituent levels are stable.

At each visit, the subject will receive 150% of their baseline cigarettes per day. Providing additional cigarettes per day will allow for potential compensatory smoking or a potential delay in attending the brief clinic or curbside appointments. Menthol and non-menthol cigarettes will be provided, as preferred.

5.2 Assessing Smoking Behavior

Smoking inhalation measures will be performed at visits 00 & 6 on a subset of subjects. The device provides valid and widely used objective measures of inhalation. Inhalation: Inductance plethymography will be done using the BioRadio Wireless Physiology Monitor (https://glneurotech.com/bioradio/) analyzed by the VivoSense Complex Respiration Analysis software (http://vivonoetics.com/products/vivosense/). This is a dual band device that is placed over the upper chest and abdomen that records respiration as a continuous stream to memory for download and analysis. The data is analyzed for metrics such as tidal volume, inspiratory volume and time, expiratory volume and time, and flow-volume loops. This system has been validated

and is widely used for focusing on respiratory disease. The spent cigarette filter (cigarette butt) from the session will be collected.

Study Procedures

5.3 Telehealth Visit Scheduling Requirements:

Scheduling window for Phase 1 usual brand baseline screening (93) to baseline (92) visit is 7 days (+ 7 days). If the subject is unable to schedule within 30 days, they will be re-consented, but will maintain the original assigned Subject Identifier.

Scheduling window for Phase 2 weekly adaptation visits (92) to randomization (00) visits is 7 days (+4) days.

Scheduling window for Phase 3 weekly visits for Week 1-6 is 7 days (-3/+4) days.
Follow-up (Week 10) scheduling window is 70 days from Week 00 visit (-3/+21).

5.4 Orientation and Screening Phase – Visit 93 and 93a

Cigarette smokers will be screened for eligibility with a brief telephone screener. Eligibility criteria will be aimed towards being inclusionary to ensure generalizability of results to a broader population of smokers. If subjects meet the initial telephone screening eligibility criteria for the study, they will be asked to participate in a more thorough screening via a virtual remote visit using telehealth technology.

Orientation: The purpose of the orientation is to inform the subjects about the study protocol. The Researcher will review the study via telehealth technology with a PowerPoint detailing the study purpose, procedures and risks. The subject is provided a copy of the consent form and HIPPA for review. After the subject has been able to ask questions and receive answers and show comprehension, the consent form and HIPPA will be electronically signed or paper copies mailed back to the Researcher. Signed copies will be provided to the subject at their first brief clinic or curbside visit.

Screening: After obtaining informed consent, basic information and screening questionnaires will be completed to further screen for eligibility.

93. Screening Procedures (see Table of Procedures page 45)**:**

A. Physiological Measures:

1) Measures will be taken during the brief in-person visit 93a (see below).

B. Surveys – link sent to participant to complete REDCap based survey:

Screening forms

1) Demographics (including items needed for Masonic Cancer Center registration).

2) Brief Medical History Questionnaire to assess current diagnoses, symptoms and past health problems including psychiatric and substance abuse and medication use.
    a. Concomitant Medication: Current use and use within the prior 30 days.
    b. Date of last menstrual period and length of cycle will be acquired to assess pregnancy status.
3) Patient Health Questionnaire (PHQ/Prime-MD) will be used to assess current symptoms of depression and anxiety. BDI-II and or GAD7 will be administered for clinician to review if positive for depression or anxiety.
4) Contemplation Ladder to assess readiness of smoking cessation.
5) NIAAA Alcohol Use Questionnaire (12 month version)
6) Nicotine Dependence Questionnaire
7) Drug Use Questionnaire (1 month version)

C. *Interviews - Research Assistant interviews participant and enters directly into REDCap (except Identification Form):*

1) Tobacco Use History and Nicotine Exposure Questionnaire
2) Brief Medical History Follow-up form (completed as needed by study staff to further assess current diagnoses, symptoms or past health problems).
3) Tobacco Use 7 Day Followback Form for cigarettes per day, alcohol and marijuana
4) COVID-19 Related Questions
5) An Identification Form: includes name, address, email, phone number, age and date of birth. This information will be stored separately from any other study data and in a password protected database. This information will not be shared with any other study investigators.
6) End of Visit Evaluation

After the telehealth visit, medical review will be conducted by the licensed medical professional and eligibility criteria will be confirmed. If eligibility criteria appear to be met, the participant will be enrolled in the Daily Interactive Text Response (ITR) for data collection via REDCap (described below). If the subject shows compliance with providing the daily ITR data for 5 days, they will attend a brief, in-person visit to complete the screening.

93a In-Person Screen

Physiological Measures:

Prior to the appointment, the COVID Assessment will be completed via phone call. The vitals and carbon monoxide (CO) measures will be taken during the in-person screening visit (93a) using the monitors that will be provided for home use. The subject will receive training on use of the devices and staff will observe the procedure to verify accurate technique and assess competence.

1) Height and weight
2) Carbon monoxide will be collected using iCO Smokerlyzer, a portable carbon monoxide monitor that can be used at home with a smartphone.
3) Blood pressure and heart rate is assessed with the at home monitor provided.

4) A spot urine sample will be collected for a pregnancy test [hCG detection] for female participants of childbearing potential to confirm eligibility.
5) Participants may be asked to provide 3 of their usual brand cigarettes for ventilation testing.

If the carbon monoxide level, blood pressure and heart rate are within the guidelines, the participant will be considered eligible to enroll. If the CO is below 8ppm, a nicotine check strip may be used to verify regular smoking status.

In addition, biological sample collection supplies and handouts will be provided.

Daily Interactive Text Response (ITR) System and Data Management

At the Screening visit (93), eligible subjects will be trained to use the Daily Text (ITR) system. The ITR system uses a stand-alone REDCap project, in conjunction with Twilio (REDCap approved service provider) to send automatic survey invitations to the participant's phone via a text message. Participants will receive a text message each day throughout the study with a unique link to the REDCap survey. The survey will ask for the previous day's number of cigarettes (both study and non-study cigarettes), use of any other tobacco or nicotine products, marijuana and alcoholic drinks.

To be enrolled in the recording system, research staff must enter subject initials, telephone number, subject identifier and start dates into the HIPAA compliant REDCap project. Identifying information (initials and telephone numbers) will be marked as identifiers and not allowed to be extracted with the data by the Bioinformatics group.

Any missing data due to incomplete or entry errors (e.g., subject entered 88 study cigarettes rather than 8 study cigarettes) will be reviewed at the next visit via the Timeline Follow-back method and compiled in the ITR Review Form. This data will be integrated into the ITR as revised data. The original subject entered data will also be retained in the ITR database.

5.5 Phase 1: Baseline Smoking Usual Brand

During Phase 1, (Screening Visit 93a through Visit 92), eligible subjects will purchase their own cigarettes and smoke their preferred brand as usual. Data will be collected during a telehealth visit and biological sample for biomarker analysis will be collected at the brief clinic or curbside visit (see below).

Procedures for Baseline 1 Telehealth Visit (92)

A. Physiological Measures and Biomarker Samples

1) Vital signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit
2) Carbon monoxide level will be obtained while conducting the telehealth visit.

3) Biological sample collection to assess for nicotine and carcinogen metabolites. A first void urine sample will be collected the morning of the visit and saliva will be collected during the telehealth visit. Samples will be dropped off at the brief clinic or curbside visit.

B. Surveys – link sent to participant to complete REDCap based survey:

Biomarker Modifier Questionnaires:

1) Environmental Tobacco Smoke Questionnaire

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale(MNWS)
2) Questionnaire of Smoking Urges-Brief Scale – Usual Brand (QSU)
3) Respiratory and Global Health Questionnaire
4) Modified Cigarette Evaluation Scale – Usual Brand
5) Perceived Health Risk
6) Cigarette Purchase Task – Usual Brand
7) Duke Sensory Questionnaire – Usual Brand
8) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety.
9) Tobacco Policy Support Questionnaire

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily ITR Review form (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire (since last visit)
7) Intention to Quit
8) Drug accountability: Complete Dispensing Logs for study cigarettes to be dispensed at brief clinic or curbside visit
9) Study Compliance Review
10) End of Visit Evaluation

Dispensing Study Product:

At the brief in-person clinic or curbside visit, the participant will be provided the ventilated study cigarettes. The subject will receive instruction on how to track the use of their study cigarettes for the Daily ITR. The subject will be allocated 150% of their baseline usual brand cigarettes per day. Allocating an additional 50% will allow for compensatory smoking behavior and provide a cushion for possible late visits. A nominal amount of money for each unused pack of cigarettes that are returned will be provided in order to disincentivize wasteful use of cigarettes (sharing with friends, hoarding cigarettes). Subjects who return unopened packs of their study cigarettes will receive a $2 credit per pack that will be paid out at the follow-up visit, with a max credit up to $30.

5.6 Phase 2: Adaptation to Ventilated Study Cigarette

During Phase 2 (baseline 92 to randomization visit 00), eligible subjects will be provided study ventilated cigarettes. Subjects will be instructed to continue to report on daily intake of tobacco and nicotine products, alcohol and marijuana in the ITR. Data will be collected during telehealth visits and biological samples for biomarker analysis collected at the brief clinic or curbside visit.

Procedures for Visit Telehealth Visit (Visit 91)

A. Physiological Measures:

1) CO level will be measured while conducting the telehealth visit.
2) Vitals signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.

B. Surveys – link sent to participant to complete REDCap based survey:

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale(MNWS)
2) Questionnaire of Smoking Urges-brief scale - Study Cigarette (QSU)
3) Modified Cigarette Evaluation Scale – Study Cigarettes
4) Respiratory Symptoms and Global Health Questionnaire
5) Duke Sensory Questionnaire – Study Cigarettes
6) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety.

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily IVR Call Review (follow-up on missing and unusual reports)
6) Timeline Follow Back Questionnaire
7) Intention to Quit
8) Drug accountability: Complete Dispensing Logs
9) Compliance Review
10) End of Visit Evaluation.

Supplies, sample collection containers and handouts will be provided to the participant at the Baseline 91 brief clinic or curbside visit for collection of cigarette butts, urine, saliva and blood spots for the Week 0 baseline sample collection. Participants will be asked to collect cigarette butts 24 hours prior to Visit 00.

Procedures for Visit 2 Telehealth Visit (Visit 00)

At the second Baseline visit (00), subjects will be informed that they have been randomized to either ventilated or unventilated study cigarettes. Subjects will complete several measures and provide biological samples for biomarker analysis as described below.

A. *Physiological Measures and Biomarker Samples:*

1) Vitals signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.
2) Carbon monoxide level will be obtained while conducting the telehealth visit.
3) Biological sample collection for analysis of nicotine and carcinogen metabolites will be collected prior to (first void urine sample) or at the telehealth visit (saliva and possibly blood spots) and then dropped off at the brief clinic or curbside visit. Oral cells will be collected during the telehealth, in-person curbside or clinic visit. Subjects will be instructed to brush teeth prior to the collection.
4) Review Cigarette Butt Collection: The 24-hour collection of cigarette butts prior to this visit will be reviewed and dropped off at brief clinic or curbside visit. These spent filters will be analyzed for cigarette butt staining to inform intensity of smoking behavior.

B. Surveys – link sent to participant to complete REDCap based survey:

Biomarker Modifier Questionnaires:

1) Environmental Tobacco Smoke Questionnaire

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale(MWSC)
2) Questionnaire of Smoking Urges-Brief Scale – Study Cigarette (QSU)
3) Respiratory Symptoms and Global Health Questionnaire
4) Modified Cigarette Evaluation Scale – Study Cigarette
5) Perceived Health Risk
6) Cigarette Purchase Task – Study Cigarette
7) Nicotine Dependence Questionnaire
8) Duke Sensory Questionnaire – Study Cigarette
9) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety.

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily ITR Review (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire (since last visit)

7) Randomization to either ventilated or unventilated cigarettes - Read appropriate script
8) Intention to Quit
9) Product Accountability Log
10) Compliance Review
11) End of Visit Evaluation

Dispensing Study Product:

At the brief clinic or curbside visit, the participant will be provided their randomized study cigarettes (ventilated or unventilated). The subject will continue to be allocated 150% of their baseline cigarettes per day and receive a $2 credit per pack for each unused pack of cigarettes that are returned in order to disincentivize wasteful use of cigarettes (sharing with friends, hoarding cigarettes; max credit up to $30).

5.7 Phase 3: Assigned Study Cigarette Phase:

Subjects will be smoking the assigned ventilated or unventilated study cigarettes. Subjects will be instructed to continue to report on daily intake of tobacco and nicotine products, alcohol and marijuana in the ITR. In addition, measures as described in the Table of Procedures will be collected. At the Week 3 and 6 visits, biological samples will be collected. Study cigarettes, supplies, collection containers and handouts are dispensed prior to the respective collection weeks during brief clinic or curbside visits. Additionally, cigarette butts will be collected 24 hours prior to Week 3 and 6 visits.

Procedures for Telehealth Weeks 1, 2, 4 and 5

A. Physiological Measures:

1) Vital signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.
2) Carbon monoxide level will be obtained while conducting the telehealth visit.

B. Surveys – link sent to participant to complete REDCap based survey:

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale (MNWS)
2) Questionnaire of Smoking Urges-Brief Scale – Study Cigarette (QSU)
3) Respiratory Symptoms and Global Health Questionnaire
4) Modified Cigarette Evaluation Scale (Week 1 only) – Study Cigarette
5) Perceived Health Risk (Week 1 only)
6) Duke Sensory Questionnaire (Week 1 only) – Study Cigarette
7) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety.

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment

2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily ITR Review (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire (since last visit)
7) Intention to Quit
8) Product Accountability Log
9) Compliance Review
10) End of Visit Evaluation

Procedures for Telehealth Week 3

A. Physiological Measures and Biomarker Samples:

1) Vital signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.
2) Carbon monoxide level will be obtained while conducting the video/phone visit.
3) Biological sample collection for analysis of nicotine and carcinogen metabolites collected at the prior to (first void urine) or at the telehealth visit (saliva) to be dropped off at the brief clinic or curbside visit.
4) Review cigarette butts collection from 24 hours prior to the visit. These spent filters will be dropped off at their brief clinic or curbside visit and analyzed for cigarette butt staining to inform intensity of smoking behavior.

B. Surveys – link sent to participant to complete REDCap based survey:

Biomarker Modifier Questionnaires:

1) Environmental Tobacco Smoke Questionnaire

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale (MNWS)
2) Questionnaire of Smoking Urges Brief Scale – Study Cigarette (QSU)
3) Respiratory Symptoms and Global Health Questionnaire
4) Modified Cigarette Evaluation Scale- Study Cigarette
5) Perceived Health Risk
6) Duke Sensory Questionnaire – Study Cigarette
7) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety.

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily ITR Review (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire (since last visit)
7) Intention to Quit
8) Product Accountability Log
9) Compliance Review

10) End of Visit Evaluation

Dispensing study product for Weeks 1-5

The participant will be provided their study cigarettes at the brief clinic or curbside visit. The subject will be allocated 150% of their baseline cigarettes per day. Allocating an additional 50% will provide cushion for possible late visits and/or compensatory smoking behavior. Subjects who return unopened packs of their study cigarette will continue to receive a $2 credit per pack that will be paid out at the follow-up visit.

Procedures for Telehealth Week 6:

A. Physiological Measures and Biomarker Samples:

1) Self-reported weight
2) Vital signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.
3) Carbon monoxide level will be obtained while conducting the telehealth visit.
4) Biological samples will be collected prior to (first void urine) or at (saliva and optional collection of hair and blood spots) the telehealth visit to be dropped off at the brief clinic or curbside visit. Oral cells will be collected during the telehealth, in-person curbside or clinic visit.. Subjects will be instructed to brush teeth prior to collection.
    a) Urine pregnancy tests [hCG detection] will be performed for female participants of childbearing potential to confirm eligibility.
5) Review cigarette butts collection from 24 hours prior to the visit. These spent filters will be dropped off at their brief clinic or curbside visit and analyzed for cigarette butt staining to inform intensity of smoking behavior.

B. Surveys – link sent to participant to complete REDCap based survey:

Biomarker Modifier Questionnaires:

1) Environmental Tobacco Smoke Questionnaire

Subjective Outcome Measures:

1) Minnesota Nicotine Withdrawal Scale (MNWS)
2) Questionnaire of Smoking Urges-Brief Scale – Study Cigarette (QSU)
3) Respiratory Symptoms and Global Health Questionnaire
4) Perceived Health Risks
5) Modified Cigarette Evaluation Scale – Study Cigarette
6) Cigarette Purchase Task – Study Cigarette
7) Nicotine Dependence Questionnaire
8) Duke Sensory Questionnaire – Study Cigarette
9) BDI-II and or GAD7 will be administered for clinician to review if monitored for depression or anxiety
10) Contemplation Ladder

11) Tobacco Policy Support Questionnaire
12) End of Study and Feasibility Questionnaire

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events
4) Concomitant Medications
5) Daily ITR Review (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire (since last visit)
7) Intention to Quit
8) Product Accountability Log
9) Compliance Review
10) Smoking Cessation Counseling
11) End of Visit Evaluation

Dispensing study product

None

Cessation Materials at End of Intervention

At the end of the 6 week experimental period, subjects will be strongly encouraged to stop smoking and set a quit date and if possible, stop using all tobacco products. A treatment manual for cessation will be provided and subjects will be encouraged to call the state telephone quit line. Nicotine replacement products (1 box of choice of nicotine gum, lozenge or patches) will be provided to those setting a quit date.

5.8 Brief In-Person Clinic or Curbside Visits

A brief in-person visit will be scheduled following each of the telehealth visits. Depending on the circumstances, participants may have a brief in-person clinic or a curbside visit. If clinic visits are not optimal (due to COVID-19 prevalence/restrictions, use of public transportation or if a participant is not interested in being seen in the clinic) curbside contact will be arranged. The visits should be scheduled to occur as soon as possible after the telehealth visit. If the visit cannot be scheduled within 24 hours, a partial telehealth visit will occur to update the record. For the brief clinic or curbside pick-up, participants will be required to have a mask of either their own, sent by staff or provided one and told to wear it during the visit. Staff will wear PPE as required (optional if vaccinated. Any sample collection supplies, containers and other handouts will be provided at this time.

During the brief clinic or curbside visit, subjects will drop off the appropriate biosamples, cigarette butts and collect the week's supply of study cigarettes and return empty packs. If there have been device issues with the vitals or CO monitors, they can troubleshoot at this visit.

Biosamples to be returned at this visit:

1) First morning void urine collection (Weeks 92, 00, 3, 6, Early Terminating (ET) if applicable)
2) Saliva sample obtained for nicotine metabolite ratio-NMR (Week 92)
3) Saliva sample for TNEs (Weeks 92, 00, 3, 6, ET if applicable).
4) Blood spot (Weeks 00, 6); this collection is optional.
5) Hair sample (Week 6); this collection is optional.
6) Cigarette butt collection (Weeks 00, 3, 6)

Procedures to be conducted at this visit:

1) Oral cells will be collected during the telehealth, in-person curbside or clinic visit. Subjects will be instructed to brush teeth prior to arrival at the visit.
2) Inhalation measures (Weeks 00 and 6) will be conducted on a subset of subjects.

5.9 Follow-up

Procedures for Follow-up Telehealth Visit Week 10

Follow-up will occur 4 weeks after the end of the experimental period. Tobacco use status (amount and type of tobacco product use) will be determined. Quitting smoking or staying quit will continue to be strongly encouraged. The following procedures will only involve checking records of product use, vital signs and questionnaires. There is no in-person visit at Week 10.

A. Physiological Measures:

1) Vital signs (blood pressure, heart rate) will be obtained while conducting the telehealth visit.
2) Carbon monoxide will be obtained while conducting the telehealth visit.

B. Surveys – link sent to participant to complete REDCap based survey (optional – RA enter direct into REDCap):

Subjective Outcome Measures:

1) Respiratory Symptoms and Global Health Questionnaire
2) Nicotine Dependence Questionnaire

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Events (close out any open events)
4) Concomitant Medications
5) Tobacco Use 7 Day Followback Form
6) Smoking Cessation Counseling
7) End of Visit Evaluation

5.10 Early Termination

Procedures for Early Termination Telehealth Visits

If a subject decides to withdraw from the study prior to completion or if they are withdrawn by the Project Leader due to safety concerns, they will be scheduled for an early termination visit. If the participant is contacted within the window of a regularly scheduled visit, all measures for that visit will be collected. If the early termination visit occurs at Weeks 1, 2, 4 or 5, additional safety measures will be obtained since these measures are not scheduled at those visits. If the subject is seen outside the regularly scheduled visit window, safety measures will be obtained.

A. Physiological Measures:

1) Vital signs (blood pressure & heart rate) will be obtained while conducting the telehealth visit.
2) Carbon monoxide level will be obtained while conducting the telehealth visit.
3) Biomarker collection (first void or spot urine and saliva) collected prior to or at the telehealth visit and then dropped off at the brief clinic or curbside visit.

B. Surveys – link sent to participant to complete REDCap based survey:

The following additional assessments will be completed at early termination via REDCap, if not part of the usual measures scheduled for the regularly scheduled visit:

Subjective Outcome Measures:

1) Respiratory Symptoms and Global Health Questionnaire
2) Perceived Health Risk
3) Modified Cigarette Evaluation Scale – Study cigarette
4) Cigarette Purchase Task – Study Cigarette
5) Nicotine Dependence Questionnaire
6) Duke Sensory Questionnaire - Study Cigarette
7) Tobacco Policy Support Questionnaire
8) End of Study and Feasibility Questionnaire

C. Interviews - Research Assistant interviews participant and enters directly into REDCap:

1) COVID-19 Assessment
2) Health Changes and Menstrual Cycle Questionnaire
3) Adverse Event
4) Concomitant Medications
5) Daily ITR Review (follow-up on missing and unusual reports)
6) Timeline Follow-back Questionnaire
7) Intention to Quit
8) Product Accountability Log
9) Smoking Cessation Counseling
10) End of Visit Evaluation

5.11 Study Completion:

Any adverse events that remain open from the last study session will be discussed and closed. Once a participant has completed all study procedures and all open events have been closed or designated as ongoing at end of trial, the Site Leader will review the participant's binder and sign a form indicating study completion for that participant. If any of the measures raise concern, the Site Leader will determine if the subject should be followed further.

5.12 Product and Procedures Compliance Review Sessions

At each visit, subjects will be counseled about use of only cigarettes obtained through the study. Participants will be asked about any concerns or obstacles associated with use of the study cigarettes. The importance of honest reporting will be stressed. Participants will be told that it is crucial for them to report any use of products obtained from outside the study, even though it is discouraged. If difficulties are encountered, participants will be asked why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to problem-solve how to deal with these difficulties in order to meet the protocol requirements. Additionally, participants will be counseled about their Daily ITR text completion, telehealth visit attendance and product accountability. These review sessions should be about 5-10 minutes in length.

5.13 Quit Attempts During the Study Protocol:

At each session, we will ask the participant if he/she is currently abstaining from smoking and/or has the intention of quitting or planning to quit smoking prior to his/her next scheduled visit. If the answer is yes, they will be provided with information on local quit lines to assist them in their quit attempt and a cessation manual provided. If the subject chooses to quit during the study, they will be encouraged to do so and will be offered their choice of 1 box of nicotine replacement products (gum, lozenge or patch) to aid in their quit attempt.

If Currently Abstinent from Smoking:

- Encourage continued abstinence from smoking.
- Provide the cessation manual and local smoking cessation resources.
- Follow visit schedule and procedures.

If a Participant is Planning to Quit Smoking, But Has Not Initiated the Quit Attempt

- Ask if a target quit date has been chosen and document the target quit date.
- Provide the participant with the cessation manual and local smoking cessation resources.
- Recommend that on the target quit date he/she puts any tobacco products "away" so as to avoid unwanted cues to smoke

At the end of the 6-week experimental period, all subjects will be strongly encouraged to stop smoking and if possible, using all tobacco products, and set a quit date. A treatment manual for cessation will be provided and subjects will be encouraged to call the state telephone quit

line. A box of nicotine replacement (e.g., gum, lozenge or patch) will be provided to those who have a quit date or have quit smoking.

5.14 Compensation for Clinical Trial

Participants will be compensated $30 for the initial telehealth screening visit and $10 for their brief in-person screening follow-up visit (CO/vital measurements and devices pick-up).They will receive $30 for the shorter visits (91, 1, 2, 4, 5 and Follow-up) and $40 for the longer visits (92, 0, 3 and 6) for a total of $380. In addition to the visit compensation, subjects will receive a $10 reimbursement for travel for each clinic or curbside visit ($100). Required biomarker samples (urine and saliva: visits 92, 0, 3, 6; buccal cells: visits 0, 6) and optional biomarker samples (hair: visit 6 and blood spots: visits 0, 6) will be compensated at $10 per sample; and cigarette butt collection at $25/collection (visit 0, 3 and 6 for maximum of $185). Payment for ITR completion will be a weekly bonus of $10 for not missing any texts ($90 maximum). A $100 bonus will be given for completion of the study. The maximum earned will be $855. In addition, money for unopened returned packs ($2/pack) will be added at the follow-up visit for a maximum of $30. A subset of participants who have been asked to participate in the addendum inhalation study will receive an additional $25 per session.

5.15 Product Compliance and Data Consistency

The importance of honest reporting by subjects will be stressed. Consistency across data collection will be examined by comparing: a) daily text records; b) Timeline Follow-back; and c) Product Accountability Logs where the amount of products dispensed will be recorded and number of unsmoked cigarettes are recorded via photos sent to us or shown during the telehealth visit. Participants will be provided feedback regarding the consistencies across the data and encouraged to be more accurate if the data are inconsistent. In the event that subjects uses non-study cigarettes (e.g., purchased or provided by a friend), they will be asked to report the type and amount of product to us. Also, self-reported abstinence will be biochemically confirmed by tobacco nicotine equivalents (TNE) for abstinence from all nicotine-containing products. No biochemical verification methods exist to determine if smokers used their usual brand cigarettes in addition to the research cigarettes. Therefore, we will encourage accurate reporting of any cigarettes or nicotine products.

6 Data Collection

Subject information including name and date of birth, race/ethnicity, and information about participation in this study will be entered into a secured database at the time of registration. The primary source of study data will be the protocol specific electronic case report forms. Research related results will not be placed in the participant’s medical record. Data related to study participation will be collected and retained in REDCap and through the ITR Daily Text system. Subjects will directly enter their responses to surveys into REDCap’s HIPAA secured website. In the event that REDCap is not functioning, the assessments will be completed as soon as REDCap is available. Other source documents will be kept in the participant’s electronic binder and the interviewer will save the data in Box or upload as pdf to REDCap. Biosamples will be tracked via Biomarker Management Website on REDCap. Databases will be maintained indefinitely.

6.1 Questionnaires and Other Measures

The following measures will be obtained. Some forms are administered only at baseline to assess history and eligibility criteria and others are repeated measures:

Questionnaires:

1) *Tobacco Use History and Exposure*, derived from the Population Assessment of Tobacco and Health (PATH) assesses the generalizability of our study subjects allowing comparisons with a nationally representative sample of smokers which measures variables such as smoking rate (current and maximum), cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking and history of use of other tobacco and nicotine products.
2) *Demographics* inquiries about age, gender, race, ethnicity, current occupation and usual occupation, and income.
3) *Brief Medical History* includes current health status for current diagnoses, symptoms, and past health problems including psychiatric and substance abuse and medication use.
   - Medical History Follow-up Questionnaire will be completed by study staff to further assess current diagnoses, symptoms or past health problems.
4) *Patient Health Questionnaire-PHQ (Prime-MD)* assesses depression and anxiety symptoms, a brief questionnaire developed for evaluation of mental disorders by primary care physicians.[14]
5) *Beck Depression Inventor*y 2nd Edition[15] (BDI-II) is a severity measure assessing symptoms of depression and will be administered if the PHQ is positive for any diagnoses or if monitoring for depression.
6) *Generalized Anxiety Disorder GAD-7* is used for rapid screening for the presence of a clinically significant anxiety disorder (GAD, PD, SP & PTSD), especially in outpatient settings.[16]
7) *Concomitant Medications Questionnaire* will assess prescription, over-the-counter medications and supplements used 30 days before the screening and throughout the clinical trial.
8) *COVID-19 Assessment* will assess current symptoms or potential exposure to a person who has tested positive for COVID-19.
9) *End of Visit Questionnaire* asks about any issues encountered during the visit or concerns about the participants compliance with the protocol.

Biomarker Modifier Questionnaires

1) *Environmental Tobacco Smoke Exposure Questionnaire* consists of 1 question related to tobacco smoke exposure at home, work and socially.

Subjective Outcome Measures

The following measures will be obtained according to Table of Procedures.

Subjective Outcome measures:

1) *Interactive Text Response (ITR)* record the amount of cigarettes and other tobacco and nicotine containing products on a daily basis. Also recorded is use of marijuana and alcohol.

2) *Timeline Follow-back*[17] will be used at each visit to assess tobacco and nicotine intake not assessed on the ITR and alcohol and marijuana use. Cigarettes (study and non-study) per day missing from ITR texts (or errors needing correction) will be collected in ITR Review form.
3) *ITR Review Form assesses* study and non-study use of cigarettes missing from the ITR texts, correct errors in ITR entries or clarify any discrepancies or unusual ITR reports.
4) *Nicotine Dependence Questionnaire* for usual brand or study cigarettes includes questions from the Fagerström Test for Nicotine Dependence (FTND);[18] Brief Wisconsin Inventory of Smoking Motives (WISDM) Primary Dependence Motives subscale;[19] and several PATH dependence items.
5) Minnesota Nicotine Withdrawal Scale (MNWS) is an 8 item assessing symptoms of tobacco withdrawal.[20]
6) *Questionnaire of Smoking Urges* is a 10 item scale measuring urge to smoke.[21]
7) *Contemplation Ladder* evaluates readiness to quit.[22]
8) *Adverse Events Scale* assesses the nature, severity, duration, action taken, and outcome of adverse events related to tobacco product use
9) *Respiratory Symptoms and Global Health Questionnaire* rates cough, phlegm production, shortness of breath and other respiratory symptoms along with a rating of current overall health.
10) *NIAAA Alcohol Use Questionnaire* (*12 month*) assesses frequency and quantity of alcohol use.[23]
11) *Drug Use Questionnaire (1 month)* assesses amount, frequency in past year, past month and date of last use of drugs.
12) *Perceived Health Risk* assesses perceived health risks of no tobacco use, usual brand of cigarettes.[24]
13) *Modified Cigarette Evaluation Scale (mCES)* measures different dimensions of responses to cigarettes (e.g. psychological reward, satisfaction, aversiveness, and additional oral and respiratory sensation items.[25-27] The modified scale has 7 additional questions.
14) *Cigarette Purchase Task* for behavioral economics measures purchase tendency for cigarettes based on price.[28]
15) *Duke Sensory Questionnaire* a questionnaire rating it for liking, satisfaction, and estimated nicotine delivery. Subjects also rated the strength of each puff in different regions of the respiratory tract comprising the nose, tongue, back of the mouth and throat, windpipe, and chest. Ratings were made using a 7-point scale ranging from not at all (0) to extremely.[29]
16) *Intent to Quit Questionnaire* assesses whether a quit date has occurred or a quit date is planned before the next visit.
17) *End of Study and Feasibility* Questionnaire an open-ended questions administered at the Week 6 or Early Termination visit which enquires about the subject's knowledge, attitudes and beliefs about the study cigarettes, reactions to a policy that bans ventilation, ideas about how this policy should be conveyed to the public and what needs to be in place to reduce any negative effects. Subject response will be coded for consistency in themes and categorized and evaluated in an exploratory way. The feasibility portion is a questionnaire that asks the subject to rate the degree of difficulty

or ease with completing the subjective measures, collecting carbon monoxide and blood pressure and collecting of biological samples.

18) *Tobacco Policy Support Questionnaire* assesses subject's opinion on potential tobacco control policies.

6.2 Biological Specimens

Biological samples will be collected and brought to the clinic or curbside visits for biomarkers analysis. Subjects will be asked to collect urine and saliva sample at weeks 92, 00, 3 and 6 visits for biomarker assessments. Buccal cells will be collected during the telehealth, in-person clinic visit or curbside at weeks 0 and 6. Blood spots (optional) will be collected at weeks 00 and 6. Hair collection will be optional and collected at week 6. These optional samples will be used to determine the feasibility of collection and analytic capabilities and concordance of results across biosample type. Participants who have experienced extensive hair loss will be exempt from the hair sample collection. The optional biosamples collected over the duration of the study will be at the discretion of the lead PI's. This would occur if it is determined that one type of biomarker has a negative impact on recruitment (e.g., few people willing to collect hair sample) or we find the sample(s) collected do not yield sufficient biomarker levels. Cigarette butts (24-hour collection) will be collected at visits 00, 3 and 6 and the butts from the inhalation measures.

Samples will be stored in a -20 or -80°C freezer. Specimens will be collected, stored at sites and shipped to the Masonic Cancer Center at intervals upon request from the lead site.

The samples may be stored until they are used up or no longer needed up to a maximum of 10 years from the study's end. A subject has the right to withdraw consent at any time by informing the Principal Investigator by following the instructions provided in the HIPAA document. If this occurs any remaining identifiable research sample(s) will be destroyed.

Rationale for choice of biomarkers:

The biomarkers for this project have been selected to represent exposures to carcinogens. We have chosen 2 types of biomarkers found in saliva, blood spots or hair. The first is related to nicotine intake, namely total nicotine equivalents (TNE). Knowing that smokers adjust their smoking behavior to maintain nicotine exposure, it is important to understand if this occurs when smoking an unventilated cigarette (e.g., complete or partial compensation). Also, because tobacco carcinogens are increased with filter ventilation, the consideration of intake of these carcinogens are important to understand in the context of the nicotine intake. Thus, the other validated biomarker, NNAL, was selected to represent exposure to carcinogenic tobacco specific nitrosamines because this is a known lung carcinogen. DNA adducts N6-hydroxymethyl-deoxyadenosine and N2-ethylidene-deoxyguanosine derived from formaldehyde and acetaldehyde, respectively. DNA adducts will be analyzed in buccal cells. Buccal cells (cells gently scraped from the inside of the cheek with a cytobrush) can serve as a minimally invasive tool to measure the responses to tobacco and can be leveraged to determine the biological effects associated with tobacco- and nicotine-related toxicant exposure.

Biomarker Analysis:

The following biomarkers has been selected to represent exposures to nicotine and carcinogen, NNK:

1) Nicotine: Total nicotine equivalents – TNE (molar sum of nicotine and its metabolites) in urine will be used primarily to assess overall cigarette exposure. For subjects who state they are no longer smoking, we will confirm cigarette-free days and abstinence from all tobacco products with TNE. TNE was selected because it accounts for 73-96% of the nicotine dose and is a useful measure of daily nicotine exposure. Nicotine metabolite ratios can also provide other important information, such as differences in nicotine metabolism rate. Cotinine and 3-hydroxycotinine will be measured in saliva and blood spots for comparison across the different assays.

2) Biomarkers of Carcinogen Exposure have shown good laboratory reproducibility, have clear differences in levels between smokers and nonsmokers and/or decrease upon tobacco cessation, and reflect differences in toxicants in the various tobacco/nicotine products.[30,31]

   a. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its N- and O-glucuronides (exposure to tobacco-specific lung carcinogen NNK) in urine and possibly hair or blood spots.
   b. Tobacco specific oral and esophageal carcinogen N′-nitrosonornicotine (NNN) and its N-glucuronide in urine.
   c. Phenanthrene tetraol and 3-hydroxy phenanthrene (exposure to and metabolism of the representative polycyclic aromatic hydrocarbon phenanthrene) in urine.
   d. Mercapturic acids (exposure to acrylonitrite (CEMA), acrolein (3-HPMA) and crotonaldehyde (HMPMA) in urine.
   e. DNA adducts N6-hydroxymethyl-deoxyadenosine and N2-ethylidene-deoxyguanosine derived from formaldehyde and acetaldehyde, respectively. DNA adducts will be analyzed in buccal cells

3) Inflammatory and Oxidative Stress Biomarkers

   PGE-M and 8-*iso*-$PGF_{2\alpha}$ in urine will be measured to assess inflammation and oxidative stress.

4) Other biomarkers

   a. Untargeted metabolomics also will be measured in the urine by gas chromatography and mass spectroscopy. This is an emerging technology that provides a broad screen for exposures and cellular responses that represent biomarkers of exposure and potential harm. They will be employed for the analysis of urine to identify novel biomarker profiles distinguishing exposures from ventilated and non-ventilated cigarettes for totality of cigarette smoke-derived exposures and enodgenous cellular responses.[32,33]
   b. Exhaled carbon monoxide (CO) collected at every clinic visit.
   c. In addition, other tobacco-related validated biomarkers for assessment in urine, saliva, buccal cells, hair or blood spots may be developed over time and these additional

assays will be completed as appropriate using samples stored in the Biobank. Also, in the future, samples may be analyzed for metabolism of tobacco toxicants or nicotine and tobacco-related exposures or harm.

5) Spent Filter Analysis:

Filters will be collected at Week 00, Week 3 and after 6 weeks on study cigarettes. They will be analyzed for constituent yield and filter ventilation blocking and may also be used for filter staining analysis. For extraction of spent cigarette filters, one-cm portions will be removed from the mouth end of the spent cigarette filters, stripped of the wrapping paper and transferred into clean vials for constituent extraction. Filters will be analyzed for nicotine, TSNA, and PAH. Cigarette butts will be collected the day before visit 00, 3 and 6.

Biomarker Specimen Tracking:
The Biomarker Management Website will be using REDCap for tracking biomarker samples. All samples will be scanned into the website at the study site thereby tracking initial collection and then scanned into Excel and uploaded to REDCap, prior to shipment of samples. Samples will be scanned into Excel and uploaded to REDCap, upon receipt at the UMN Masonic Cancer Center Tobacco Labs.

7 Risks to Subjects and Others

Potential risks of participation include the following:

1) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to severe or fatal medical problems including:

   a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
   b. Respiratory Diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
   c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia
   d. Diabetes
   e. Immune function, rheumatoid arthritis
   f. Other Health Risks Associated with Smoking: Including but not limited to infertility, ectopic pregnancy, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction; age-related macular degeneration, blindness and cataracts.

2) Smoking assigned study cigarettes: Cigarettes similar or identical to research cigarettes are currently on the market, therefore, the major side effects associated with research cigarettes are similar to usual brand cigarettes. In addition to the above medical problems, participants may experience some minor adverse health effects such as headaches, dizziness, nausea, sore irritated throat, or increase in cough using the unventilated cigarettes. Due to free study cigarettes, there could be an increase in the number of cigarettes smoked per day. This rate of smoking may persist after completing the study.

Smoking the study cigarettes does not provide any less risk than their usual brand cigarette and could pose increased health risks. Participants may also experience increases in levels of carbon monoxide, a gas from smoke. Should an increase in smoking behavior occur, guidelines have been developed for terminating subjects from the study to avoid a marked increase in cigarettes smoked.

3) Medicinal Nicotine (nicotine polacrilex and transdermal patch) if requested for use while quitting smoking: Most common adverse effects for medicinal nicotine include irregular heartbeat/palpitations, high blood pressure, mouth sores, mouth or throat irritation, heartburn, upset stomach, vomiting, diarrhea, dizzy or lightheadedness, and hiccups or belching. Additional adverse effects associated with nicotine gum include teeth or jaw problems. Additional adverse effects associated with nicotine patch are erythema, pruritus, edema and sleep disturbance. There may also be a risk of nicotine toxicity including symptoms such as nausea, dizziness, vomiting, diarrhea, and weakness.

4) Changes in blood pressure and/or heart rate: Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate.

5) Smoking and oral contraceptives in women: Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking.

6) Risk to Fetus**:** Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), and early childhood behavioral problems.

    1) Avoiding Risks to Fetus: If female participants choose to be sexually active, they are asked to use an appropriate “double barrier” method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge in addition to male use of a condom), or should be using prescribed “birth control” pills, injections, or implants. Female participants with child-bearing potential will be tested for pregnancy at baseline visit 91 and week 6 or early termination. They will be asked about their pregnancy status and date of last period to confirm status at all other visits.

7) Smoking and medications: Quitting smoking can greatly benefit participants’ health. However, changes in smoking can lead to changes in metabolism of some medications. Subjects should disclose all medications they are taking. We also recommend that participants discuss any planned or actual changes in how much they smoke with their physician, especially if they are taking any medications for psychiatric, cardiovascular, or other serious diseases.

8) Survey Questionnaires: The questionnaires will include medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could make the subject feel uncomfortable.

9) Obtaining blood pressure: Researchers may find out the participant has abnormal blood pressure and refer the subject to their primary care physician. In addition, the blood pressure cuff may cause minimal discomfort.

10) Breach of Confidentiality: There is a slight risk of loss of privacy if other people find out the results of the individual subject's interview or other tests.

11) Other: Risk of exposure to COVID-19 if using public transportation for an in-person visit.

Risks to Others

Tobacco products in the home can be toxic to children and pets. Smoking can lead to secondhand exposure that can increase risk for disease. All participants will be informed to keep products inaccessible to children and pets and informed about the harms of secondhand smoke and vapor exposures in the home or in cars.

8 Potential Benefits of Participation

There are no immediate benefits from participating in the study. Whereas no assurance can be made to an individual subject that he/she will personally benefit from such research, the experience should be beneficial by providing a better understanding of their smoking behavior. The risks compared to potential benefits are minimal to the individual research subject and virtually nonexistent to other or society in general.

Importance of knowledge gained:

The information obtained from this type of study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health. The benefit to society may be potentially significant if the end result from this study is to determine the potential feasibility and impact of banning ventilated cigarettes as a public policy measure.

9 Adverse Event Reporting, Safety Monitoring and Withdrawal of Subjects

9.1 Identifying Adverse Events

While participating in the trial, adverse events and concomitant medications will be assessed at every study visit and vital signs and carbon monoxide will be obtained. Medical events will typically be identified during the administration of the Health Changes Questionnaire and Respiratory Health Questionnaire. Other events may be identified from physiological study measures or by spontaneous reports during assessments.

Questionnaire items that will be reviewed to assess the occurrence of an Adverse Event:

Health Changes Questionnaire: If the participant answers **'YES'** to **Questions 1, 2, 3b** or **3c** , the interviewer should assess for adverse events.

1) Have you had any negative changes in your physical or mental health since your last visit?
2) Have you received any form of medical care?
3) Have you had any changes in medication since your last visit?

Respiratory Health Questionnaire: If the participant indicates **'YES'** to regarding having a cold or flu the interviewer should assess for adverse events.

Vital signs will be reviewed:

Blood Pressure:

- The 'Adverse Event Log' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** second automatic blood pressure measurement during the same visit is **at or above 160 systolic or 100 diastolic.**
- The 'Adverse Event Log' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** second automatic blood pressure measurement during the same visit **is below 90 systolic or 50 diastolic and the participant is experiencing symptoms** listed on the 'Blood Pressure and Heart Rate Symptom Checklist.'

Heart Rate:

- The 'Adverse Event Log' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** second automatic heart rate measurement during the same visit is **at or above 105 bpm.**
- The 'Adverse Event Log' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** second automated heart rate measurement during the same visit is **below 45 bpm and the participant is experiencing symptoms** listed on the 'Blood Pressure and Heart Rate Symptom Checklist.'

Attribution of Adverse Events:

- Unrelated: The AE is clearly **NOT related** to the intervention
- Remotely (Unlikely) likely: The AE is **doubtfully related** to the intervention
- Possibly related: There is a reasonable possibility the AE **may be related** to the intervention
- Definitely Related: The AE **is clearly related** to the intervention
- Unknown: The AE is **not easily associated with** the intervention, concomitant medications, health states or personal norms. The cause is uncertain.

9.2 Withdrawal or Monitoring of Participants

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1) Cardiovascular disease (CVD) event: Typically include*s* MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5) Pregnancy: If a participant becomes pregnant during the study she will be withdrawn from the study if using tobacco products. A pregnancy will trigger an 'Adverse Event' to be documented and this event will remain open until delivery. If the participants agrees, approximately 30 days after being withdrawn or reporting a positive pregnancy test, the research staff will call the participant to confirm her due date. The licensed medical professional will follow-up with the participant after delivery to ask questions about the baby's health and will update the open Adverse Event.
6) Diagnosis of severe COVID-19: If a participant reports a positive test or symptoms consistent with the diagnosis and experienced significant illness (e.g. hospitalization) they will be withdrawn from the study.

The following will be monitored and can lead to the participant being withdrawn by the PI or Licensed Medical Professional:

1) Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-enrollment: 1) BP is at or above 160 systolic or 100 diastolic, 2) BP is below 90 systolic or 50 diastolic **and the participant is experiencing symptoms** listed on the Blood Pressure and Heart Rate Symptom Checklist, 3) HR is at or above 105 bpm, 4) or below 45 bpm **and the participant is experiencing symptoms** listed on the Blood Pressure and Heart Rate Symptom Checklist.
2) Medication changes: If a participant begins taking any of the exclusionary medications or other medications that could potentially have a smoking-drug interaction post-enrollment, the medical professional will determine how best to monitor and minimize potential risks (including withdrawal if warranted). We will provide a letter to the participant that can be given to the prescribing physician and that lists potential medications that can be affected by changes in smoking that could occur as a result of participation in the study.
3) Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical professional to determine whether continued participation in the study is appropriate.
4) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then the PI can withdraw him/her from the study at the PI's discretion.

5) If there is reason to believe the participant is sharing large quantities of the study cigarettes with other people.

Withdrawal Procedures

If the decision to withdraw a subject occurs at a study visit, regular procedures will be conducted as well as the additional early termination procedures described in 6.7. If it is determined via a phone call that withdrawal is appropriate or if the subject is dropping out, we will ask the subject to attend an exit telehealth visit to complete questionnaires, product accountability and safety assessments and to receive their final study payment.

If the subject refuses an exit visit, we will request that at the minimum, product accountability be completed. We will also stress the importance of being able to assess safety measures for the subject's safety.

9.3 Management of SAEs and Other Study Risks

Subjects will be screened for any potentially compromising medical condition and will be monitored throughout the study. Subjects who experience any adverse side effects of concern will be reviewed by the study's licensed medical professionals, sent to the emergency clinic or referred to their physician, depending on the nature and severity of the adverse event. Subjects will be encouraged to quit smoking and optimally all tobacco use at the end of study and we will conduct a 4 week follow-up to assess tobacco use status. If necessary, we will continue follow-up to make sure that no greater harm is experienced by the subject and to continue to encourage quit attempts. If biomarker analysis determined significantly greater exposure to toxicants than prior to the study, the subject will be contacted to discuss the results and cessation of all tobacco products will be strongly recommended.

The site medical professional will review all AEs. A study participant may be discontinued from the study if the medical professional and/or PI determine it is the best decision in order to protect the safety of a participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an AE/SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes. Any AE that remains open will be reviewed and closed at the 30 day follow-up interview.

9.4 Reporting of SAEs to the IRB, FDA, and NCI

Serious or unexpected adverse events (SAE or SUSAR) as defined in 21 CFR 312.32 (death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices), other serious events (important medical outcomes) that are related or possibly related to study participation will be reported to the Administrative Core, all site IRBs (annually unless a Reportable Event), the NCI Project Officer, FDA, and the Data Safety and Monitoring Board. Site IRBs require that fatalities related to the study be reported promptly.

Reports of all unexpected product related SAEs will also be documented within FDA's SAE data monitoring system, within 72 hours

Reporting of IRB Actions to NCI

Actions taken by the local IRBs in response to SAEs will be reported to NCI in the annual noncompetitive continuation application, as will reports of changes or amendments to the protocol as a result of an SAE. Recommendation for trial discontinuation, significant changes or amendments to the protocol, or other significant findings as a result of an SAE will be reported immediately to the NCI Project Officer by the Project PI.

Reporting Changes or Amendments to the Protocol

Any changes or amendments to the protocol made in response to adverse events/SAEs will be reviewed by PIs and then requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. The DSMB, FDA and NCI will be notified about any significant changes to the protocol. NCI will be informed of any approved changes in protocol by documentation in the noncompetitive continuation application. Changes that significantly alter the scope of the research or the ability of the research to achieve its specific aims will be submitted to the DSMB, FDA, and NCI for approval prior to implementation.

10 Statistical Considerations

10.1 Trial Endpoints

Primary Endpoint:

- The change in total NNAL from visit 00 to week 6 visit.
- The mean CPD based on 7-day IVR data between week 00 and Week 6 visit

Secondary Endpoint:

- Change in TNE, CEMA, and PheT from visit 00 to week 6 visit
- Change in intensity of smoking measured by filter analysis collected at 00, Week 3 and Week 6.
- Change in parameters of inhalation depth measured at 00 and Week 6.
- Change in subjective measures (dependence as measured by the FTND, mCES, and Perceived Health Risk) from visit 00 to Week 6 visit.

Exploratory Endpoints:

- Change in biomarkers of other volatile organic compounds (e.g.,3-HPMA, HMPMA) from visit 00 to Week 6 visit.
- Determine concordance in biomarkers of exposure across different sample collection methods.

Secondary Endpoint
Safety Endpoints:

- Adverse Events (AEs)

- Serious adverse events (SAEs)

Randomization

Subjects will be randomly assigned using a stratified (by site), block randomization scheme into the following groups: (1) ventilated filter cigarettes; or (2) unventilated filter cigarettes.

Sample size and power considerations

To determine the sample size for a test of non-inferiority for unventilated filter cigarettes compared to ventilated filter cigarettes (control group), we used pilot data from our original ventilated/unventilated study 1 (Hatsukami, personal communication). For the purposes of sample size considerations, we will focus on total NNAL as one of the primary outcomes. Seventy subjects had a baseline NNAL value while smoking their usual brand and 19 and 16 subjects had an end of study NNAL value for the ventilated and unventilated groups, respectively. The endpoint of interest is the change in NNAL from baseline. To normalize the distribution of NNAL, the calculations were performed in the log scale. The non-inferiority margin (NIM) was set at a 15% change between groups. This criterion was chosen because it is close to, but not greater than the upper limit of the 95% confidence interval (CI) for the geometric mean of the change in NNAL. Therefore, 73 subjects per group will achieve 80% power to detect non-inferiority for the mean change in NNAL using a one-sided, two sample t-test with a significance level of 0.05. Furthermore, with these sample sizes, a one-sided, two-sample t-test for the mean difference in cigarettes per day (CPD) from baseline will have 90% power to determine non-inferiority with a significance level of 0.05 if the NIM is 2 cigarettes. A mean difference between ventilation groups of less than 2 cigarettes is considered to be in the range of equivalence. To accommodate a 10% loss-to-follow-up rate, we plan to enroll 81 subjects per group for a total of 162.

Study Populations

Intent-to-treat

The first analysis of all primary and secondary endpoints will adhere to the intent-to-treat principle. Under this principle, all subjects randomized to one of the two study arms will be included in the analysis in the group to which they were randomized regardless of protocol violations and compliance to treatment assignment.

Per-Protocol

A second per-protocol analysis will include only participants who complete the 6 week visit without protocol violations or non-compliance.

10.2 Statistical analysis plan

The primary objective of the statistical analysis is to compare the effects of cigarette ventilation between two study groups: ventilated filter cigarettes and unventilated filter cigarettes. All statistical analyses will be performed using SAS version 9.4 (SAS Institute Inc., Cary NC) and a p-value less than 0.05 will be considered significant.

Describing the Study Population

Descriptive statistics will be performed for data collected on demographic characteristics, subjective measures and biomarkers at different phases and visits. Baseline data will be compared between the two ventilation groups with the two-sample t-test or the non-parametric Wilcoxon rank sum test for continuous or ordinal variables and chi-square tests for categorical variables. Biomarker data may be log transformed if necessary.

Primary Endpoint Analysis

The primary endpoints are (1) the total NNAL at the 6-week visit adjusted for NNAL at end of Phase 2 (visit 00); and (2) the mean CPD based on 7 days ITR data before week 6 visit adjusted for the mean CPD during Phase 2 (visit 00). The analysis of these two endpoints will evaluate non-inferiority of the unventilated group compared to the ventilated group.

Primary Analysis

The primary analysis will be a one-sided, two-sample t-test for non-inferiority. The null hypothesis for total NNAL (analyzed in the log scale) is that the increase from end of Phase 2 (visit 00) is 15% greater in the unventilated group compared to the ventilated group. The NNAL alternative hypothesis is that the increase from baseline (visit 00) is no higher than 15% in unventilated over ventilated groups. If the null hypothesis is rejected in favor of the alternative hypothesis, we will conclude that the unventilated filters are no more harmful in terms of NNAL exposure than the ventilated filter and may actually be less harmful. Similarly for the CPD, the non-inferiority t-test will have a null hypothesis that the 6 week mean increase in CPD from end of Phase 2 (visit 00) for the unventilated group is greater than 2.0 cigarettes compared to the ventilated group. The alternative hypothesis is that the CPD increase in the unventilated group is no more than a mean of 2.0 cigarettes verses the CPD increase in the ventilated group and the unventilated group may even smoke fewer cigarettes.

Secondary Analysis

The above methods will be supplemented with multiple linear regression analysis to include the baseline (visit 00) value for NNAL or CPD and the stratification variable (site), plus any other subject specific characteristics which might not be balanced between the study groups (p-value<0.2).

Finally, NNAL and CPD will be analyzed for all visits, starting at visit 00, using a linear mixed effects model (SAS PROC MIXED). The fixed effects are ventilation group indicator, plus other potential predictors. To model the variation within subjects, several candidate variance-covariance structures will be compared using both graphical and information criteria. Variance parameters will be estimated using restricted maximum likelihood method with the Satterthwaite approximation. This analysis will provide useful information about the change in toxicant exposure and the change in the number of cigarettes smoked per day over time.

Both linear regression models and repeated measures analysis can be modified for the equivalence and non-inferiority testing situations.[34]

Secondary Endpoint Analysis

The secondary analyses include the other biomarkers (as listed above). The analysis for these potential toxicants will be the same as that outlined above for NNAL with measurements at end of Phase 2 (visit 00) and at the 6 week visit. A non-inferiority margin has not been established for many of these biochemical measures. Instead, group differences or ratios (if in the log scale) will be estimated with their 95% CI and examined as to whether or not they contain 0 for differences or 1 for ratios. Inhalation measures and smoking intensity (solanesol levels in the filter butts) will be analyzed with similar methods as the change in biomarker and CPD with regression models incorporating covariates for baseline variables that may be different between groups (p-value<0.2). The FTND as a measure of dependency is a composite score that ranges from 0 to 10. With the expectation of non-inferiority for the unventilated group, a linear regression model for FTND at 6 weeks will include the FTND at baseline (visit 00) and the ventilation group indicator, plus any other important subject characteristic. The 95% CI for the estimated coefficient for the group indicator will be calculated to verify that it contains the value zero, indicating no difference in dependency between ventilation groups. The mCES and PHR questionnaires produce a series of subscales. To identify differences between ventilated and unventilated groups, non-parametric methods will be utilized, first with the Wilcoxon signed rank test to check for changes from end of Phase 2 to 6 weeks within each ventilation group and then with the Wilcoxon rank sum test for differences between groups.

Exploratory Analysis

The exploratory analysis for the other volatile organic biomarkers (listed in section 6.2) will be the same as that outlined above for NNAL and the other secondary biomarkers.

Correlation procedures (Pearson and Spearman) will measure the degree of association for the same biomarkers assayed from two or more biosamples.

Safety Endpoints

AEs and SAEs will be recorded as described in the Adverse Event SOP. AEs and SAEs will be tabulated separately for the two groups. We expect study product-related AEs and SAEs to be rare in this trial and, therefore, no formal statistical comparison of the rate of AEs and SAEs across treatment groups is planned for this trial.

Missing Data

Every effort will be made to limit the amount of missing data in this trial. Study participants will be incentivized to attend study sessions. That said, some level of missing data is inevitable in a study of this kind. We will compare subjects who do and do not complete the study sessions in order to identify baseline covariates associated with study completion.

Our primary approach to handling missing data will be a sensitivity analysis using multiple imputation with the Markov Chain Monte Carlo (MCMC) method[35] carried out in PROC MI in SAS, where missing values are imputed using regression models developed from baseline covariates. Values can be imputed for both continuous and categorical variables. If the ventilation groups are associated with missing data, we will conduct multiple imputation for each ventilation group separately. Following imputation, standard statistical methods can be applied. A final single

assessment of ventilation group difference will be obtained from combining the results across the imputed datasets using PROC MIANALYZE in SAS.

Interim Analyses

No interim analysis is planned.

11 Supporting Documentation and Operational Considerations

Informed Consent Procedure and Documentation

Potential subjects will be told the nature of the research over the phone during screening and then at a virtual orientation meeting where the study is described in detail. All potential study participants will be provided a copy of the IRB-approved consent form to review prior to signing. They will be told they may discontinue participation at any time and will not be discriminated against if they choose to do so. Subjects will be told their participation in the project will be strictly confidential, that any identifying information will be available to the project investigators or institutional or federal regulatory groups only, and that no identifying information concerning the data and results will be made known. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. Subjects will be required to demonstrate an understanding of the study purpose and procedures prior to signing the consent form. If the participant decides to participate in the study, he/she will be asked to sign and date the consent document and will receive a copy for their records. Consent form must be signed before the research is started.

Confidentiality of Data

Participation in the project will be strictly confidential, any identifying information will be available to the project investigators and institutional or federal regulatory groups only, and no identifying information concerning the data and results will otherwise be made known. All raw data will be coded with numbers and any form with identifying information (e.g. consent forms) will be kept electronically in a password protected database. Subjects will have written assurance that while de-identified individual subject data may be available to other researchers for research purposes, only a summary of the results will ever be published or otherwise publicly released. Identifying information (initials and telephone numbers) entered in the Daily Text system will not be shared nor extracted with the data by the Biostatistics and Data Management Core.

All data will be de-identified and posted on a secure, password-protected website that is only available to research investigators (both inside and outside the institutions affiliated with the Program Project Grant) due to data sharing requirements; subjects will be informed of this during the informed consent process.

The data from these studies will not be used to direct patient care. Therefore, participation in this study will have no influence on the care the subject receives nor will it influence treatment decisions. If subjects would like their information on vitals or other findings released to another party, they will be asked to sign a release of information form.

To help protect the participant's privacy, a Certificate of Confidentiality from the National Institutes of Health is in place. With this certificate, the researchers cannot be forced to disclose information that may identify the participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the participants, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the Federal Food and Drug Administration (FDA).

The Certificate of Confidentiality does not prevent the participant or a member of their family (e.g. guardian) from voluntarily releasing information about themselves and their involvement in the research. If an insurer, employer or other person obtains the participant's written consent to receive research information, then the researcher may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without consent, information that would identify the individual as a participant of the research project in instances such as evidence of child or elder abuse or a participant's threatened harm to self or others.

Data Security

All electronic data will be de-identified, housed on the University of Minnesota AHC secured server. In–house access will be password protected. De-identified outcome data will be posted on a secure, password-protected website that is only available to research investigators. All identifying information will be kept separate from the data in a locked, secure place at the local site. Research study staff are required to complete site specific data security training through their institutions. There will be *no* data or consent forms placed in subject's medical records.

Data Management

Data for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly backups retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data).

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, SFTP, etc.). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data. Key study personnel are trained on the use of these platforms and will comply with protocol specific instructions.

Data Integrity: Adherence to Protocol Procedures and Training

Standard Operating Procedures will include overall study procedures and visit procedures will be provided. Extensive training for research personnel will occur at a remote site initiation visit prior to the study start, where the protocol and procedures will be carefully described. Case Report Forms will be electronic to maximize parallel recording of data across studies and allow for remote access. Each visit will have a checklist of all the measures that need to be administered and the order by which these measures are administered. All subjective forms will be provided on web-based REDCap including the telephone screening. Additionally, conference calls will be held regularly with lead site, PIs and coordinators to review project status, accruals, and procedures. The project manager from UMN will monitor the study remotely and possibly monitor in–person at OSU once COVID travel restrictions are lifted to review study procedures, audit the documents and observe study visits. Data on REDCap will be monitored by UMN for missing data or any unusual value through data quality checks.

11.1 Data and Safety Monitoring Plan (DSMP)

See the full Data and Safety Monitoring Plan document for complete information.

At each of the sites, the site PI and licensed medical professional will conduct regular conference calls or virtual meetings with the study staff to review patient’s progress and their experiences with the tobacco products, including any adverse events. Entrance criteria will be reviewed following screening. Medical history will be reviewed by the medical professional for any contraindications for the use of the study cigarettes and out of range vital signs checked at each visit. Subjects will be under medical supervision while in the study and contacted on an ongoing basis by our research staff who will assess adverse events and make appropriate referrals to the medical staff. The study coordinator (with direction from the medical professional) at each of the sites will be responsible for the daily oversight of subject safety. The Data and Safety Monitoring Board (DSMB) and other regulatory bodies will be informed of any adverse events either at the regularly convened meetings or in the annual report, or if necessary, immediately.

The DSMB for this center will review the protocol and establish guidelines for data and safety monitoring. This will include developing standard procedures for day-to-day monitoring by the internal monitors, investigators and study staff. This Board will meet at regular intervals (at least once a year) to evaluate the progress of the trial, review data quality, recruitment, study retention, and examine other factors that may affect study outcome. They will also review the participants' ability to achieve the study requirements and the rates of adverse events to determine whether there has been any change in participant risk. Their review will ensure that subject risk does not outweigh the study benefits. A brief report will be generated from each of these meetings for the study record and forwarded to the Institutional Review Boards (IRB).

The DSMB will be available to convene outside of the regular meetings, if necessary, if concerns should arise regarding a particular subject, or any troublesome trends in the subject experiences. They will make appropriate recommendations for changes in protocol, if needed.

The University of Minnesota and The Ohio State University NCI designated Cancer Center also has a Cancer Protocol Review Committee that meets on a monthly basis to review all cancer-related protocols. This study will be subjected to review by this committee. Progress reports to this committee are submitted on at least a yearly basis.

All product-related adverse events of a non-serious nature will be reported to the IRB at the time of renewal. Reportable serious and related adverse events will be reported by telephone or email to the IRB within the 5 days of our receipt of information regarding the event and written reports will be submitted within 10 days. The DSMB will review all serious or unexpected adverse events and provide recommendations.

NCI will be informed of any significant action taken as a result of the DSMB's findings. Subjects will be informed of any changes in risk.

Record Retention

The investigator will retain study records including source data, copies of case report form, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

12 Conduct of the Study

Good Clinical Practice

The study will be conducted in accordance with the appropriate regulatory requirements. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

Duration of Study Participation

A subjects' direct study involvement is approximately 13 weeks:

Phase 1: Baseline ~1 week;
Phase 2: Ventilated Study Cigarette - 2 weeks
Phase 3: Intervention: Unventilated or Ventilated Study Cigarette - 6 weeks
Follow-up: One visit 4 weeks post intervention.

Study sites

The sites will be University of Minnesota-Twin Cities (PI: Dorothy Hatsukami) and The Ohio State University (PI: Peter Shields)

Subject Identifier

Project and Site Identifier:
8 = University of Minnesota
9 = Ohio State University

Subject ID:
UMN: 8001 – 8350
OSU: 9001 – 9350

Data Collection Time Points Identification Numbers:
93 = Screening
92 = Phase 1: Baseline
91 = Phase 2: Ventilated study cigarettes
00 = Phase 3: Randomization to ventilated or unventilated
01 = Week 1 visit
02 = Week 2 visit
03 = Week 3 visit
04 = Week 4 visit
05 = Week 5 visit
06 = Week 6 visit - End of Intervention visit
10 = Week 10 Follow-up visit
86 = Early Termination Visit
98 = Additional Visit

Procedure Table	Platform	SCRN 93	BL-92	BL-91	BL-00	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Follow-Up 10	Early Term
			UB	Phase 2		Phase 3 INTERVENTION							
Phone Recruitment Questionnaire	REDCap/Interview	X											
VISIT ASSESSMENTS													
Weight & height (92 only)	REDCap/Interview	X											
Vitals (blood pressure & heart rate)[1]	REDCap/Interview	X	X	X	X	X	X	X	X	X	X	X	X
Carbon Monoxide[1]	REDCap/Interview	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Screen [hCG detection]	REDCap	X									X		
Compliance Review	Progress Note		X	X	X	X	X	X	X	X	X		
Intention to Quit	REDCap/Survey		X	X	X	X	X	X	X	X	X		X
Smoking Cessation Counseling[2]	Progress Note										X	X	X
VISIT FORMS													
Concomitant Medications	REDCap/Survey	X	X	X	X	X	X	X	X	X	X	X	X
Health Changes Questionnaire	REDCap/Interview		X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment	REDCap/Interview		X	X	X	X	X	X	X	X	X	X	X
Randomization	REDCap/RA				X								
Product Accountability Log	REDCap/RA		X	X	X	X	X	X	X	X	X		X
End of Visit Evaluation	REDCap/RA	X	X	X	X	X	X	X	X	X	X	X	X
SCREENING QUESTIONNAIRES													
Tobacco Use and Exposure History	REDCap/Interview	X											
Identifying Information	REDCap/Survey	X											
Demographics for MCC Registration	REDCap/Survey	X											
Demographics	REDCap/Survey	X											
Brief Medical History	REDCap/Survey	X											
PHQ (PrimeMD)[3]	REDCap/Survey	X											
Alcohol Use Questionnaire 12 mo.	REDCap/Survey	X											
Drug Use Questionnaire 1 mo.	REDCap/Survey	X											
BIOMARKER MODIFER QUESTIONNAIRE													
Environmental Exposure Question	REDCap/Survey		X		X			X			X		
TOBACCO USE MEASURES													
ITR Daily Text	ITR (RC/Twilio)		X	X	X	X	X	X	X	X	X		X
ITR Review	ITR (RC/Twilio)		X	X	X	X	X	X	X	X	X		X
Timeline Follow-back	REDCap/Interview		X	X	X	X	X	X	X	X	X		X

Procedure Table	Platform	SCRN 93	BL-92	BL-91	BL-00	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Follow-Up 10	Early Term
			UB	Phase 2		Phase 3 INTERVENTION							
Tobacco Use 7 Day Followback Form		X										X	
ADVERSE CONSEQUENCES													
MNWS	REDCap/Survey		X	X	X	X	X	X	X	X	X		
QSU - Usual cigarettes	REDCap/Survey		X										
QSU - Study cigarettes	REDCap/Survey			X-V	X-V	X	X	X	X	X	X		
Respiratory Symptom Questionnaire	REDCap/Survey		X	X	X	X	X	X	X	X	X	X	X
OTHER MEASURES													
Nicotine Dependence Questionnaire	REDCap/Survey	X-UB			X-V						X-SC	X-UB	X-SC
Contemplation Ladder	REDCap/Survey	X									X		
Covid-19 Symptom Questionnaire	REDCap/Interview	X	X	X	X	X	X	X	X	X	X	X	X
End of Study Questionnaire	REDCap/Survey										X		X
ACCEPTABILITY MEASURES													
Cigarette Eval. Scale Usual brand	REDCap/Survey		X										
Cigarette Eval. Scale Study cigs	REDCap/Survey			X-V	X-V	X		X			X		X
Perceived Health Risk	REDCap/Survey		X		X-V	X		X			X		X
Cigarette Purchase Task-Usual Cigs	REDCap/Survey		X										X
Cigarette Purchase Task-Study Cigs	REDCap/Survey				X-V						X		X
Duke Sensory Questionnaire	REDCap/Survey		X	X-V	X-V	X		X			X		X
Tobacco Policy Support Questionnaire	REDCap/Survey		X								X		X
OTHER													
Cigarette Butt Collection	REDCap/RA				X			X			X		
Inhalation Measures	REDCap/RA				X						X		
BIOMARKERS[4]													
Total Nicotine Equivalents	BMW (REDCap)		X		X[5]			X			X		X
Total NNAL	BMW (REDCap)		X		X[5]			X			X		X
N HOCH-dAdo and N ethylidene-dGuo	BMW (REDCap)		X		X[5]			X			X		X
Phet & 3-PheOH	BMW (REDCap)		X		X[5]			X			X		X
Mercapturic acids[6]	BMW (REDCap)		X		X[5]			X			X		X
8-iso-PGF and PGE-M	BMW (REDCap)		X		X[5]			X			X		X

Procedure Table	Platform	SCRN 93	BL-92	BL-91	BL-00	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Follow-Up 10	Early Term
			UB	Phase 2		Phase 3 INTERVENTION						-	
Metabolomics	**BMW (REDCap)**		X		X[5]			X			X		X
2 (4.5ml) Biorepository	**BMW (REDCap)**		X		X[5]			X			X		X
BIOSAMPLES													
Saliva NMR	**BMW (REDCap)**		X										
Urine	**BMW (REDCap)**		X		X			X			X		X
Saliva	**BMW (REDCap)**		X		X			X			X		X
Buccal cells	**BMW (REDCap)**				X						X		
Blood Spot	**BMW (REDCap)**				X						X		
Hair Sample	**BMW (REDCap)**										X		

[1]CO and vital signs will be measured by participant at home with devices provided by the study; CO and vitals for eligibility is collected at 93a In-Person Screen. [2]If quit date prior to Week 6, self-help materials & NRR will be offered; [3]If PrimeMD or CES-D positive, Beck or GAD administered; [4]Urine & Saliva at Week 92, 00, 3, 6; Buccal Cells at Week 00 and 6; Optional: Blood Spots at Week 00 and 6; Hair at Week 6 only. Specific types of biosamples collected over the duration of the study will be at Lead PI discretion; [5] Week 00 is collected as a back-up baseline sample. [6]Mercapturic acids of acrolein (3-HPMA), benzene, crotonaldehyde (HMPMA), & acrolonitrile

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