VERMONT CENTER ON TOBACCO REGULATORY SCIENCE

PROJECT 4, STUDIES 1 & 2*:

LOW NICOTINE CONTENT CIGARETTES IN VULNERABLE POPULATIONS: PREGNANT WOMEN

STUDY PROTOCOL

Version 12: 3/MAY/2022

(* Note that NCT04033237, "Project 4, Study 2: Extended Exposure to Low Nicotine Content Cigarettes in Pregnant Women," is Study 2 in this document.)

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Abbreviations

- VLNC: Very low nicotine content
- RNC: Reduced nicotine content
- NNC: Normal nicotine content
- CPD: Cigarettes per day
- CO: Carbon monoxide
- BP: Blood pressure
- HR: Heart rate
- BPM: Beats per minute
- BMI: Body Mass Index
- NMR: Nicotine metabolite ratio
- NNN: *N*'-nitrosonornicotine
- NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
- BDI: Beck's Depression Inventory
- OASIS: Overall Anxiety Severity and Impairment Scale
- MINI: Mini International Neuropsychiatric Interview
- FTND: Fagerström Test for Nicotine Dependence
- WISDM: Wisconsin Index of Smoking Dependence Motives
- MNWS: Minnesota Nicotine Withdrawal Scale
- QSU: Questionnaire of Smoking Urges
- CES: Cigarette Evaluation Scale
- CPT: Continuous Performance Task
- EDC: Electronic Data Capture
- CPT: Cigarette Purchase Task
- Brief-A: Behavioral Rating Inventory of Executive Function
- EQ-5D: Euro-Qol
- TPQ: Time Perspectives Questionnaire
- D-KEFS: Delis-Kaplan Executive Function System
- DDT: Delayed Discounting Task
- WASI-II: Wechsler Abbreviated Scale of Intelligence-II
- SST: Stop Signal Task

- FeNO: Fractional Exhaled Nitric Oxide
- 3 HC: 3-hydroxycotinine
- COT: Cotinine

Project Protocol

Objective:

The primary overall objective of these studies is to evaluate the use and effects of cigarettes varying in nicotine content. This study will examine the two lowest doses (0.12 mg and 0.03 mg) compared to the pregnant smokers' usual brand. Study 1 will use a within-subjects design to compare effects of cigarettes varying in nicotine content on (1) reinforcing efficacy, (2) compensatory smoking, (3) amelioration of abstinence-induced craving and withdrawal, (4) smoker preference for NNC vs. RNC cigarettes in a behavioral-economic preference test when all cigarettes are available at equal response cost, and (5) smoker preference for NNC vs. RNC cigarettes when NNC are available under progressively-increasing response cost. Study 2 will evaluate the effects of extended exposure to cigarettes differing in nicotine content in pregnant smokers with < an Associate's degree. This study will be limited to two conditions: usual brand versus the 0.03 mg dose. After a baseline period in which daily smoking rate and other baseline assessments are completed, participants will be randomly assigned to usual brand or the VLNC condition and followed weekly for 12 weeks.

Background Information:

The 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA) gives the Food and Drug Administration (FDA) regulatory authority over tobacco products, including nicotine levels in cigarettes. That is an exciting development as it creates the opportunity to examine the Benowitz and Henningfield (1994) hypothesis that smoking prevalence, nicotine dependence, and smoking-related morbidity and mortality can be lowered substantially by reducing the nicotine content of cigarettes to non-addictive levels. Computer modeling predicts that reducing nicotine levels in cigarettes would produce substantial improvements in population health (Tengs et al., 2005). An essential initial step towards the implementation of such a policy is to thoroughly investigate its safety and potential unintended adverse consequences. Indeed, the FDA's Center for Tobacco Products seeks to establish research centers to assist with the mission of investigating such regulatory matters related to the FSPTCA (see RFA-DA-13-003). The FDA explicitly notes that researching tobacco regulatory questions in vulnerable populations is a crosscutting agency priority, listing women of childbearing age (15-44) and pregnant women among the vulnerable populations of interest.

Approximately 23% of U.S. women of childbearing age are regular cigarette smokers, with prevalence being considerably higher among socioeconomically disadvantaged women. Indeed, disadvantaged women are at increased risk for smoking, nicotine dependence, using high nicotine yield cigarettes, and, perhaps most importantly, for smoking during pregnancy. Not surprisingly, disadvantaged female smokers are also at significantly increased risk for smoking-related adverse health consequences, including cervical cancer, thrombosis related to hormone-based contraception, infertility, and early menopause. Specific to smoking during pregnancy, disadvantaged women are at substantially increased risk for catastrophic pregnancy complications, fetal growth restriction, and adverse birth and neonatal outcomes. Studies testing an innovative regulatory strategy of reducing the nicotine content of cigarettes to a non-addictive level (i.e., <0.2 mg nicotine) have shown promising beneficial effects (decreased smoking rate, reduced toxicant exposure, and increased cessation) in the general population of smokers. However, these studies have uniformly excluded vulnerable populations, especially

pregnant women, who may respond differently considering their greater vulnerability to smoking and nicotine dependence. Thus, little is known scientifically about how this highly vulnerable subgroup of smokers might respond to a nicotine reduction policy.

Public health concerns regarding smoking among disadvantaged women, especially during pregnancy, are growing (DHHS, 2001; Higgins & Chilcoat, 2009; Kandel et al., 2009; WHO, 2010). We are proposing to study less educated women (< an Associate's degree) because they are at increased risk for (a) smoking, (b) nicotine dependence, (c) smoking during pregnancy, and (d) use of high nicotine yield cigarettes (SAMHSA, 2010). These characteristics render this population a highly vulnerable group with regard to the potential of abusing and suffering adverse health consequences from tobacco products, including very low nicotine content (VLNC) cigarettes, where there is potential for severe craving and withdrawal, possibly resulting in compensatory smoking or use of multiple tobacco products in an effort to protect a desired nicotine-blood level. Any of these outcomes would be of particular concern among pregnant women because of the risks to the developing fetus. Conversely, this population also has the potential to benefit substantially from lowering the nicotine content of cigarettes through reduced toxin exposure, lower dependence severity, higher likelihood of quitting, and lower risk to the fetus among those who smoke during pregnancy. To our knowledge, there is no empirical information on the effects of VLNC cigarettes in pregnant women.

Overall, the proposed project will provide a rigorous experimental analysis of the effects of brief and extended exposure to very low nicotine cigarettes in disadvantaged pregnant women, which should provide critically important new information to the FDA on this vulnerable group of smokers.

Theoretical context:
Little is known about specific effects that very low nicotine-content (VLNC) cigarettes may have in women. We know of no studies of VLNC cigarettes specifically in women. However, as we review below, VLNC cigarettes produce a promising profile of effects that appear to support the Benowitz and Henningfield (1994) hypothesis. As such, they have the potential to substantially improve women's health.

Brief-exposure studies. Laboratory studies conducted with male and female smokers in the general population consistently find that acute use of VLNC cigarettes reduces abstinence-induced cigarette craving and withdrawal (e.g., Buchhalter et al., 2005; Johnson et al., 2004; Pickworth et al., 1999). When VLNC cigarettes are the only cigarettes available in lab-based behavioral economic tests, they are readily self-administered at rates and in patterns that are indistinguishable from normal nicotine-content (NNC) cigarettes (Shahan et al., 1999). However, when a NNC cigarette is available in addition to the VLNC cigarette in direct preference tests, smokers show a strong preference for the higher-dose option (Shahan et al., 1999; Johnson et al., 2004). Importantly, though, when both types of cigarettes were available but the response requirement for the higher-nicotine cigarette was progressively increased, analogous to constraining availability of the higher-nicotine cigarette, consumption of VLNC cigarettes increased (i.e., functioned as an economic substitute; Johnson et al., 2004).

Extended-exposure studies. More recently, three studies have examined extended exposure to VLNC

cigarettes among relatively more educated and healthy male and female smokers (Benowitz et al., 2007; 2012; Hatsukami et al., 2010). Benowitz et al. (2007) conducted an unblinded study in which smokers were tapered from 0.8 mg to 0.1 mg nicotine yield cigarettes at 1-week intervals. Plasma cotinine decreased by 70% relative to baseline, with no increase in craving. Furthermore, 25% of participants quit by the end of the 6-week study despite reporting no interest in quitting upon entering the study. Similarly, Benowitz et al. (2012) conducted a second study in which smokers were tapered using progressively lower nicotine content cigarettes, with each dose smoked for a 1-month interval. The number of cigarettes smoked per day decreased, as did cotinine levels and biomarkers of carcinogen exposure (e.g., NNAL) at the lowest nicotine-dose cigarette (0.1 mg yield/cigarette). Both Benowitz et al. studies showed compensatory smoking with intermediate-dose but not VLNC cigarettes.

In a randomized trial with smokers interested in quitting, participants were randomly assigned to one of three tobacco products with varying nicotine yield levels (0.3 mg cigarette, 0.05 mg cigarette, or 4 mg lozenge) (Hatsukami et al., 2010). They were instructed to use the assigned products for 6 weeks and to then make a quit attempt. After 6-weeks' use of the 0.05 mg nicotine yield cigarette, there was a 30% reduction in the number of cigarettes smoked per day, a 25% reduction in breath carbon monoxide (CO) levels, a 95% reduction in cotinine levels, and significant reductions in tobacco-specific carcinogens and other toxicants. These measures either did not change in the 0.3 mg condition or increased, likely due to compensatory smoking observed at that dose. Compensatory smoking was not observed among those abruptly switched to the VLNC (0.05 mg) cigarette. Importantly, smoking rates were still declining at the end of the study, suggesting the potential for more substantive reductions with longer exposure. In the proposed study on extended exposure (Study 2), we will lengthen the duration of the study period to 12 weeks to more fully characterize this time course. Whether these same patterns occur among disadvantaged women is a primary question that we are seeking to address in this proposal.

Effects of very low nicotine content (VLNC) cigarettes:

Studies of VLNC (e.g., 0.05 mg nicotine yield) cigarettes suggest that, acutely, they produce many effects in smokers that are qualitatively similar to normal nicotine content (NNC; e.g., 0.8 mg yield) cigarettes, but with somewhat reduced efficacy. VLNC cigarettes reinforce behavior (Shahan et al., 1999; Shahan et al., 2001), maintaining similar rates of self-administration as NNC cigarettes despite the fact that participants prefer NNC cigarettes when given a choice (Shahan et al., 1999). Compared to not smoking, VLNC cigarettes increase ratings of satisfaction and liking (Donny et al., 2007; Donny & Jones, 2009; Rose et al., 2000), although the magnitude of these effects is typically reduced compared to those produced by NNC cigarettes (Butschky et al., 1995; Gross et al., 1997; Robinson et al., 2000). VLNC cigarettes also reduce withdrawal and craving (Pickworth et al., 1999), although some symptoms (e.g., restlessness, impatience) may be more effectively alleviated by NNC cigarettes (Buchhalter et al., 2005). Much less is known about the effects of VLNC cigarettes over an extended period of use. When only VLNC cigarettes were available in an inpatient setting, the number of cigarettes smoked and the motivation to smoke during periods of abstinence decreased over time (Donny et al., 2007). Reductions in reinforcement in the real world, however, may prove somewhat more difficult. Outpatient smoking rate remained unchanged for a week after switching to VLNC cigarettes (Benowitz et al., 2007; Benowitz et al., 2009; Donny & Jones, 2009), but declined significantly over a period of 3-6 weeks (Hatsukami et al., 2010).

During this time, participants also reported minimal withdrawal symptoms and a reduction in nicotine dependence as measured by the FTND (Hatsukami et al., 2010). These data suggest that the conditioned reinforcing effects of cigarettes can be extinguished, but that the process is on the order of weeks rather than days. Finally, it is important to note that there is little evidence to suggest that prolonged use of VLNC cigarettes will result in a compensatory increase in smoking. Data available to date indicate that smoking is first maintained at a similar rate compared to preferred brand and then decreases over time (Donny & Jones, 2009; Hatsukami et al., 2010). Furthermore, participants tend to reduce the volume of smoke inhaled and demonstrate a decrease in expired CO (Donny & Jones, 2009; Hatsukami et al., 2010). These findings are in contrast to reports indicating an acute compensatory increase in total puff volume in participants smoking VLNC cigarettes (Strasser et al., 2007). Hence, VLNC cigarettes may produce a short-lived compensatory increase in smoking, but this effect likely dissipates quickly and is replaced by a decrease in smoke intake. Nevertheless, the study proposed below will closely monitor puff topography and markers of exposure to continue to address concerns about possible compensatory use of VLNC cigarettes.

In the context of considering a policy for low nicotine standards for cigarettes, the optimal upper limit for nicotine yields per cigarette is one that results in decreased abuse liability and exposure to nicotine and other constituents of tobacco smoke. The upper limit is expected to be less than, but likely near, the level of nicotine that results in sustained use and dependence. Benowitz and Henningfield (1994) proposed a value of approximately 0.2 mg (0.17 mg) of nicotine per cigarette as a threshold yield for establishing and sustaining addiction. More recent data support this estimate. Smoking rate for reduced nicotine content (RNC) cigarettes (i.e., above 0.2 mg but below NNC) tends to persist at the same or a somewhat higher rate than NNC cigarettes (Donny et al., 2007; Donny & Jones, 2009; Hatsukami et al., 2010). In contrast, much lower nicotine yields (e.g., 0.05 mg) result in reduced use and dependence (Donny et al., 2007; Hatsukami et al., 2010). Indeed, a 40% reduction in smoking behavior was observed over a 6-week period of smoking VLNC cigarettes with minimal experience of withdrawal symptoms, a reduction in FTND scores, and reduced exposure to the potentially harmful byproducts of tobacco (Hatsukami et al., 2010).

Despite the evidence that nicotine yield cigarettes below 0.2 mg will reduce cigarette use and exposure to smoke constituents, little data are available that have directly addressed the effect of different nicotine yields near or below this estimate. No published study has examined yields less than 0.05 mg. It is reasonable to expect that lower values could result in similar or more rapid declines in use and dependence, but possibly at the cost of increased withdrawal and reduced acceptability/compliance. At the upper end, three studies have evaluated cigarettes with yields >0.07 and ≤0.20 mg (Benowitz et al., 2007; Benowitz et al., 2009; Benowitz et al., 2012). In two of the studies, 20 participants smoked cigarettes with decreasing nicotine yield over the course of 6 weeks (1 week per yield). The third study was similar in design but nicotine yields were decreased on a monthly basis. The yields evaluated started in the usual brand range (0.8-0.9 mg) and decreased through several intermediate steps to 0.2 then 0.1 mg. Results showed that although nicotine intake progressively declined, cigarette use remained stable throughout the assessment period (Benowitz et al., 2007; Benowitz et al., 2009, Benowitz et al., 2012). Given the relatively short duration of use, the lack of a decline in smoking is not surprising and consistent with other reports of even lower nicotine yield cigarettes (Donny & Jones, 2009; Hatsukami et al., 2010).

Interestingly, one study observed a decrease in blood carboxyhemoglobin, total NNAL and polycyclic aromatic hydrocarbons at 0.1 mg (Benowitz et al., 2009) suggesting total smoke exposure was reduced, even if self-reported cigarettes per day were not. Furthermore, in both studies, nicotine dependence and subsequent use of preferred brand smoking decreased after the taper to 0.1 mg.

In sum, the available literature provides relatively little insight into the precise relationship between nicotine yield and potentially important outcomes in individuals smoking VLNC cigarettes over a prolonged period of time. The existing evidence supports the notion that nicotine yields <0.2 mg will likely produce the desired profile of effects, but additional information is needed.

Importance of Evaluating VLNC Cigarettes in this Vulnerable Group of Smokers:
The studies summarized in the prior section provide compelling evidence that VLNC cigarettes can substitute for usual brand cigarettes and that extended exposure to VLNC cigarettes may reduce smoking rate, toxicant exposure, and severity of nicotine dependence. These findings underscore the tremendous potential this innovative public policy strategy has for reducing smoking prevalence and smoking-related disease and death in the US. However, a serious limitation of these studies that is directly relevant to this proposal is that they uniformly excluded vulnerable populations. Study participants were also better educated and healthier than the average female smoker of reproductive age. For example, mean educational attainment in the studies by Benowitz et al. (2007, 2012) was ~15 years, and only 4% of participants in the Hatsukami et al. (2010) trial had < 12 yrs of education. This is not an insignificant limitation given that 60% of U.S. women smokers of reproductive age have < 12 years of education (SAMHSA, 2010). As such, it seems unwise to assume that results obtained in the general population of smokers will generalize to this vulnerable population. This is an important gap in knowledge that must be addressed to comprehensively evaluate the Benowitz and Henningfield hypothesis. Less educated female smokers have a higher than usual level of nicotine dependence and strong preference for high nicotine yield cigarettes, which may very well increase the likelihood of compensatory smoking.

Cigarettes to be assessed in this study:
The cigarettes to be used in this study were made under an NIH contract with production being overseen by the Research Triangle Institute (referred to as "Spectrum cigarettes"). NIH currently has approximately 10 million of these cigarettes (of varying types) for research purposes. The cigarettes selected for the study span the range of yields likely to produce the hypothesized effects, as described above. The Spectrum cigarettes are not currently commercially available, although they are similar in many ways to marketed cigarettes (e.g., similar manufacturing, filter, paper, etc.).

Project 4, Study 1

Study 1 will evaluate the effects of acute exposure to VLNC cigarettes in smokers of childbearing age with < an Associate's Degree. This study will use 3 conditions: usual brand, the 0.12 mg dose and the 0.03 mg dose.

Study Screening Procedures

Recruitment:

A sample size of 50 completers is proposed for this study. This study will use two sites, UVM and Johns Hopkins University (JHU). Anticipating 15% attrition, and five pilot subjects (3 at UVM and 2 at JHU) 65 participants will be enrolled (43 at UVM, 22 at JHU). Prior to study initiation and participant recruitment, IRB approval will be obtained from the University of Vermont's IRB and Johns Hopkins University's IRB. Potential participants will respond to community advertisements (local newspapers, community bulletin boards, Facebook, Craigslist, city buses, etc.) that contain a study description, link to an online survey and the name and phone number of the Research Assistant. Participants can choose to complete the pre-screening questionnaire online or by phone. If deemed eligible, those who complete the online questionnaire will be called by the Research Assistant to further discuss the study. The RA will read a script briefly explaining the study. If interested, they will be scheduled for an in-person screening interview. Those who call into the laboratory will be read a script briefly explaining the study. After verbal informed consent is received, participants will be asked questions over the phone to determine initial eligibility. If eligible and interested, they will be scheduled for an in-person screening interview. Participants will be informed that this is not a smoking cessation program and that they should quit smoking. They will be instructed to only participate in this study if they intend to continue smoking. Information on smoking cessation services available in the community will be provided if requested.

Potential participants will be instructed to bring a pack of their usual brand cigarettes and all prescription medications they are currently taking to the screening visit.

A participant must complete her in-person screening session within 30 days of completing the pre-screening questionnaire. If the participant is not able to attend the in-person screening visit in that timeframe, she will need to complete the telephone recruitment questionnaire again. Participants will be reminded to engage in their normal activities and smoking practices prior to the screening visit.

Informed Consent Process:

During the in-person screening session, study information will be presented and written informed consent will be required prior to participating in the screening session. In order to ensure adequate informed consent, participants will be asked to read the first several lines aloud (to determine literacy) and will then be given ample time to read the consent document. If the interviewer suspects the participant is not literate, he or she will have them continue reading further to confirm. Inability to read and comprehend written study materials will result in ineligibility and the interviewer will inform the participant that they are not eligible. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and her rights as a research participant will the consent form be signed and the participant undergo screening procedures.

Screening Measures

Those who consent will be screened for eligibility using the following measures:

The following physiological measures will be collected, recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1) Urine Cotinine will be collected to verify the participant's smoking status. It will be measured using NicAlert strips.
2) Weight and height will be measured to determine the participant's Body Mass Index. Weight will be measured in kilograms and height will be measured in centimeters.
3) Expired breath carbon monoxide (CO) levels will be assessed using a Smokerlyzer ED50 CO meter (Bedfont Instruments), a reliable and valid measure of recent smoking.
4) Urine Pregnancy Test (HCG detection) will be performed for all participants to confirm pregnancy. Blood pressure and heart rate will be measured using a CritiCare monitor to help the licensed medical professional determine final participant eligibility.

Biological Samples

Urine Sample for Urine Cotinine Analysis:
Participants will be asked to provide a urine sample for the analysis of cotinine. Samples will be stored in a -20°C freezer. Urine samples will be analyzed quarterly and stored at the University of Vermont.

Saliva sample for Nicotine Metabolite Ratio:
Participants will be asked to provide two saliva samples during the screening session for assessment of nicotine metabolite ratio (NMR), an indicator of CYP2A6 enzyme activity. Participants must wait 30 minutes after arrival to the lab before collecting the first saliva sample. During this time participants cannot eat, drink, chew gum or smoke cigarettes. After collecting the sample, participants will be provided with time to eat and/or drink before waiting another 30 minutes before collecting the second saliva sample. Samples will be stored at temperatures no more than -20°C. Saliva samples will be sent quarterly to the University of Vermont Laboratory for Clinical Biochemistry Research (Tracy Lab). The Tracy Lab will serve as a central repository for all saliva specimens and will be responsible for distributing specimens to the University of Toronto Tyndale Lab on a quarterly basis.

The following screening questionnaires will be participant-administered via paper and then will be entered into REDCap by the interviewer at the end of the visit:

1) Identifying Information Form will include the participant's REDCap Subject Identifier, name, address (including the county of residence), email address, phone number, age and date of birth.
    a. This form will be entered into the 'Identifying Information Database'.
        i. Identifying information will be kept in a locked file cabinet (source document) and in a password protected database (electronic version) separate from all other study data.
2) Beck Depression Inventory (BDI; Beck, Ward & Mendelson, 1961), to assess depressive symptoms.
3) Overall Anxiety Severity and Impairment Scale (OASIS; Norman et al., 2006) to assess frequency and severity of anxiety symptoms.

The following screening assessments will be administered as an interview and then will be entered into REDCap by the interviewer at the end of the visit:

1) The Mini International Neuropsychiatric Interview (MINI) suicide subscale (Sheehan et al., 1997) to evaluate suicide risk.
2) Tobacco Use History and Exposure Questionnaire, which measures variables such as smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking.
3) Smoking Cessation Therapy Use Questionnaire
4) Medical History Questionnaire to assess current diagnoses, symptoms and past health problems.
    a. The medications section will be transferred onto the 'Concomitant Medications' form and entered into REDCap.
5) Time Since Last Cigarette Questionnaire-Screening
6) MINI 6.0 Follow-up Questionnaire (if applicable)
7) MINI PLUS 6.0 Modules

The following screening assessments will be completed by the participant directly in REDCap, except where noted:

1) Demographic History Questionnaire, which will assess age, gender, ethnicity, race, education, income, marital status, and employment history.
2) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991)
3) Smoking Stages of Change Algorithm as well as a contemplation ladder to assess intention to quit smoking (DiClemente et al., 1991).
4) The Mini International Neuropsychiatric Interview (MINI 6.0) (Sheehan et al., 1990) a structured diagnostic interview to evaluate psychiatric disorders.
    a. Will be completed by participant through the In-Home Screening system supported by Medical Outcomes Systems.

In the event that the REDCap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into REDCap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and filed in the participant's binder.

Suicidality/Mental Health Monitoring

Participants who endorse any suicidal ideation questions, indicate suicidal ideation in the past month or a suicide attempt in the past 6 months as indicated on the BDI (score > 0 on question 9) or MINI suicide subscale (endorse question 3, 4 and/or 5 on the MINI suicide subscale or question 6 on the MINI suicide subscale with suicide attempt in the past 6 months) will not be eligible to participate in the study. The research staff member will contact a licensed on-site clinician for evaluation. In the event that no clinician is available, staff will put the participant in contact with the National Suicide Prevention Lifeline at 1-800-273-8255. They will also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible. Additionally, they will contact the Project Coordinator to inform her of the situation. The participant will be paid $25 and provided with local mental health resources.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Pregnant women ages 18-44 years who have < an Associate's Degree

2) Gestational age ≤ 25 weeks
3) Have a urine cotinine value of > 80 ng/ml (> 2 on NicAlert strip)
4) Be without current (within the past year) serious mental disorder that would interfere with study results or completion as determined by the licensed medical professional or PI,
5) Be sufficiently literate to complete the research-related tasks,
6) Be in good physical health without serious illness or change in health or medication in the past three months as determined by the licensed medical professional,
7) Report no significant use of other tobacco or nicotine products within the past month (more than 9 days in the past 30),
8) Provide verification of gestational age from OB/GYN at time of enrollment.

Exclusion Criteria:

1) Any prior use of Spectrum cigarettes (i.e., research cigarettes with reduced nicotine content),
2) Exclusive use of roll-your-own cigarettes,
3) Systolic blood pressure < 80 or ≥ 140 mmHg
    a. Participants failing for blood pressure will be allowed to re-screen once.
4) Diastolic blood pressure < 50 or ≥ 90 mmHg
    a. Participants failing for blood pressure will be allowed to re-screen once.
5) Breath CO > 50 ppm,
6) Heart rate is greater than or equal to 110 bpm or less than 45 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.
7) Have used nicotine replacement, bupropion or other pharmacotherapies as cessation aids in the past month,
8) Symptoms of psychosis or dementia,
9) Suicidal ideation in the past month (score > 0 on the BDI question 9 or endorse question 3, 4 and/or 5 on the MINI suicide subscale),
10) Answer "yes" to question A3g on the MINI Neuropsychiatric Interview Major Depressive Episode Module and symptoms occurred within the past month,
11) Suicide attempt in past 6 months (endorse question 6 on the MINI suicide subscale with suicide attempt in the past 6 months) or,
12) Participation in another research study in the past 90 days.

Children under age 18 are excluded because they cannot legally buy cigarettes. Those with unstable medical, psychiatric, or medication conditions (condition and/or medication changes in the past 3 months) are excluded as these symptoms could affect a participant's ability to complete the study. Examples include but are not limited to the following: angina, stroke, heart attack which occurred since phone screening, blood clots in the arms or legs for which the individual is undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy, 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. Individuals with baseline CO readings greater than 50 ppm, those with heart rate or blood pressure readings that are out of range (systolic: 80-139 mmHg; diastolic: 50-89 mmHg; HR: 45-109 bpm) and anyone who has attempted suicide in the past 6 months will be excluded from the study for safety concerns. Individuals who smoke 'roll your own' cigarettes exclusively will be excluded from the study because we will be unable to standardize their baseline smoking behavior. Individuals who have recently participated in a research study will be excluded as participation may have changed their smoking behavior, which may preclude a stable smoking baseline.

Because participants are required to complete portions of the protocol independently, they will need to be able to independently read and comprehend the study materials.

Eligibility Determination:
The research assistant will review the entire screening assessment battery for initial eligibility determination, confirming the subject meets the above described inclusion/exclusion criteria. The final eligibility of the participant will be determined by a licensed medical professional (MD, DO, NP, PA, Master's prepared RN or CRN) at each site after reviewing the Medical History Questionnaire, BDI, Mini Neuropsychiatric Interview, and the MINI suicide subscale. The licensed medical professional may meet with a participant if available and think it necessary for eligibility determination. He/she will sign off on eligibility prior to the baseline visit. If the licensed medical professional determines the participant is not medically eligible to participate in the study, has current symptomatology that would interfere with interpretation of the data or is unlikely to complete the study he/she will inform the research assistants who will contact the participant prior to the baseline visit. The licensed medical professional will not need to review the medical history forms of participants who are not eligible for other, non-medical reasons.

Once all the screening procedures have been completed, researchers will pay participants $25 for their time as long as they meet the requirements for urine cotinine levels. Those participants who do not meet these requirements will be dismissed from the study without payment. Participants who meet all other eligibility criteria, sans the medical criteria, will be scheduled for the baseline visit.

At the end of the screening session, the researcher will complete the End of Visit Evaluation Form, which will be filed in the subject's binder. This will allow the researcher to make note of any problems encountered during the visit, to track which computers were used for which tasks, and to assess the truthfulness of the participant in regards to self-report of tobacco use.

Study 1 Baseline Procedures

During the baseline session (Session 1), participants will become acquainted with the general study procedures, equipment, use of the CReSS Desktop smoking topography device (Borgwaldt, Richmond, VA) and controlled puffing regimens, and subjective effects questionnaires. Participants will arrive at the baseline visit having abstained from smoking sufficiently to achieve a breath CO level that is ≤ 50% of their baseline level (approximately 6-8 hours). The CO level obtained at Screening will be considered the baseline level.

<u>Visit scheduling requirements for the baseline period:</u>
Participants will be required to schedule the Baseline/Orientation visit within 30 days of their screening visit. If a participant still wants to be in the study after 30 days, she will need to be re-screened. This will be entered into REDCap as an 'Unscheduled Visit'. The participant will need to be re-consented but will maintain the original REDCap Subject Identifier. Participants will be asked to schedule the baseline visit at a time of day that will remain relatively consistent throughout the rest of the study.

Measures/Assessments

Physiological measures collected, recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1) Weight
2) CO (must be ≤ 50% of the level taken at screening)
3) Blood Pressure
4) Heart Rate

The following assessments will be administered as an interview and then entered into REDCap by the interviewer at the end of the visit:

1) Concomitant Medications Form
2) Health Changes Questionnaire which will assess any health changes.
3) Time Since Last Cigarette Questionnaire

The following assessments will be completed by the participant directly in REDCap:

1) Wisconsin Inventory of Smoking Dependence Motives-Brief Scale (WISDM; Piper et al., 2008), will be administered to assess nicotine dependence severity.
2) Perceived Health Risks Rating (Hatsukami et al., 2010), a measure of the perceived addictive potential and other health risks associated with cigarettes
3) Respiratory Health Questionnaire, a measure of cough, shortness of breath and other respiratory symptoms
4) Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), a measure of nicotine withdrawal
5) Questionnaire of Smoking Urges-brief scale (QSU; Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991), which measures the urge to smoke

After finishing the cigarette, participants will:

1) Provide breath CO samples and rate craving/withdrawal (using QSU and MNWS) every 15 minutes for one hour.
    a. The first CO sample should be taken 15 minutes after finishing the cigarette and then every 15 minutes thereafter for one hour.
    b. The participant will enter craving and withdrawal ratings directly into REDCap.
2) Complete the Cigarette Purchase Task (CPT; MacKillop et al., 2008), a self-report analogue of a progressive-ratio schedule that measures the relative reinforcing efficacy of cigarettes by querying how many of that day's cigarette they would consume in a day at varying prices.
    a. Will be entered directly into REDCap by the participant.
3) Complete the CES (CES; Westman, Levin, & Rose, 1992), which measures responses to cigarettes (e.g., reward, satisfaction)
    a. Will be entered directly into REDCap by the participant.

In the event that the REDCap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into REDCap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and filed in the participant's binder.

Study 1 Experimental Procedures

Study 1 will be conducted in three phases at approximately 3 sessions per week. Participants will arrive at each experimental session having abstained from smoking sufficiently to achieve a breath CO level that is ≤ 50% of their baseline level (approximately 6-8 hours), an abstinence criterion that has been used widely in tobacco research (e.g., Johnson et al., 2004; Tidey et al., 1999). Upon arrival at the laboratory, participants will provide a breath CO sample, complete questionnaires querying time since last cigarette, ratings of craving and withdrawal (measured using the QSU and MNWS), and update medical and medication information since the previous session. Should a participant not meet the CO abstinence criterion, the session will be rescheduled. Those who meet the CO criterion will then take two puffs from their usual brand cigarette, which is a commonly used procedure to equate time since last cigarette across sessions (e.g., Johnson et al., 2004; Henningfield & Griffiths, 1981). Thirty minutes after those initial puffs, the experimental session will commence. During these sessions, participants cannot eat or drink anything other than water.

Visit scheduling requirements for experimental period:

Every attempt will be made to schedule participants at approximately the same time of day as their screening visit (± 2 hours). If participants are not able to attend within the scheduling window, the session will be scheduled on the next available day within the scheduling window. Session 2 should be scheduled at a minimum of two days from the Baseline Visit (Session 1) and a maximum of 7 days. Outside of this window, study staff should seek approval from the PI or Project Coordinator. Sessions 3-9 should be scheduled at a minimum interval of every other day. The maximum timeframe allowed between sessions is one week. If a longer interval is needed between sessions, contact the PI or Project Coordinator for approval. Missed sessions must be made up within one week of the originally scheduled date unless prior approval is obtained from the project coordinator. All sessions will be scheduled consecutively and no session will be skipped unless otherwise informed by the PI or project coordinator.

Phase I

Phase 1 will consist of experimental sessions 2-4 in which we will determine the effects of cigarettes varying in nicotine yield (usual brand, 0.12 mg and 0.03 mg) on (1) extent to which they ameliorate abstinence-induced cigarette craving and withdrawal, (2) compensatory smoking/smoking topography, and (3) reinforcing efficacy. Participants will smoke one of the research cigarettes (dose order randomized across participants) using the CReSS smoking device to record smoking topography, including puff frequency, puff volume, inter-puff interval and other indices (Blank et al., 2009), but with no other constraints (i.e., *ad lib* puffing). Participants will smoke one additional research cigarette of the same dose using the CReSS machine in order to practice the controlled puffing procedure that will be used in subsequent phases. Participants will practice this procedure at each of the four sessions. Participants and staff will be blind to dose of the VLNC products, and cigarettes will be labeled by letter code (Cigarette A, B – save for usual brand). Participants will be instructed to attend to how each cigarette makes them feel and to write notes about the different cigarettes because in subsequent sessions they will have the opportunity to choose which cigarette they wish to smoke.

Measures/Assessments

Physiological Measures Collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) Weight
2) CO (must be ≤ 50% of the level taken at screening)
3) Blood Pressure
4) Heart Rate

The following assessments will be administered as an interview and then entered into REDCap by the interviewer at the end of the visit, except where noted:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Ratings of Craving and Withdrawal (measured using the QSU and MNWS)
    a. Will be entered directly into REDCap by the participant.
    b. Done at the beginning of each session.
5) Time Since Last Cigarette Questionnaire

After finishing the cigarette, participants will:

1) Provide breath CO samples and rate craving/withdrawal every 15 minutes for one hour.
    a. The first CO sample should be taken 15 minutes after finishing the cigarette and then every 15 minutes thereafter for one hour.
    b. The participant will enter craving and withdrawal ratings directly into REDCap.
2) Complete the Cigarette Purchase Task – Study Cigarette
    a. Will be entered directly into REDCap by the participant.
3) Complete the CES – Study Cigarette
    a. Will be entered directly into REDCap by the participant.

Phase 2

In Phase 2, Sessions 5-7 will compare reinforcing effects of the various nicotine-dose cigarettes when they are available at equally low response costs. Using equipment and methods that we have used previously to study reinforcing efficacy of smoking (Sigmon et al., 2003; Tidey et al., 1999), the reinforcing efficacy of two nicotine doses will be compared in each session. During these 3-hr sessions, participants will make 10 keyboard presses to obtain 2 puffs of either cigarette; there is no limit to the number of choices of either cigarette type in a session; this is a commonly used very-low-effort fixed- ratio response requirement (Lussier et al., 2005; Yoon et al., 2009; Tidey et al., 1999). Each dose pair will be evaluated once per participant, in random order and under double-blind conditions (save for comparisons involving usual brand cigarettes).

Measures/Assessments

Physiological Measures Collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) Weight
2) CO (must be ≤ 50% of the level taken at screening)
3) Blood Pressure
4) Heart Rate

The following assessments will be administered as an interview and then entered into REDCap by the interviewer at the end of the visit, except where noted:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Ratings of Craving and Withdrawal (measured using the QSU and MNWS)
    a. Will be entered directly into REDCap by the participant.
    b. Will be done at the beginning and end of each session.
5) Time Since Last Cigarette Questionnaire

Phase 3

In Phase 3, Sessions 8-9 will examine the extent to which the lowest nicotine dose (0.03 mg) functions as a substitute for the usual brand dose when the response cost for the usual brand dose progressively increases (Johnson et al., 2004). Again, doses will be tested in pairs. In these 3-hr sessions, 2 puffs of the lower-nicotine cigarette will be available at a constant low response requirement (10 keyboard presses), while 2 puffs of the usual brand cigarette will be available on a progressive-ratio schedule that begins at 10 presses and increases each time it is chosen, using a progression used in our prior studies (160, 320, 640, 1280, 2400, 3600, 4800, 6000, 7200, 8400, etc.) (Sigmon et al., 2003; Tidey et al., 1999). There is no limit to the number of choices of either cigarette type in a session. We will calculate cross-price elasticity for each dose to quantify the degree to which it serves as an economic substitute for the usual brand cigarette (Johnson et al., 2004).

Measures/Assessments

Physiological Measures Collected, recorded on paper, and entered into REDCap by interviewer at the end of the visit:

1) Weight
2) CO (must be ≤ 50% of the level taken at screening)
3) Blood Pressure
4) Heart Rate

The following assessments will be administered as an interview and then entered into REDCap by the interviewer at the end of the visit, except where noted:

1) Concomitant Medications
2) Medical Event Form, if applicable
3) Health Changes Questionnaire
4) Ratings of Craving and Withdrawal (measured using the QSU and MNWS)
    a. Will be entered directly into REDCap by the participant.
    b. Will be done at the beginning and end of each session.

5) Time Since Last Cigarette Questionnaire
6) Cigarette Purchase Task – Study Cigarette
    a. Two CPTs will be completed (one for each cigarette type).
    b. Will be entered directly into REDCap by the participant.

Participant Compensation:
Participants can earn up to $1400 in this study. They will receive $25 for completing the screening visit, plus an additional $20 bonus for completing the visit on time as scheduled. Payment will be made regardless of enrollment as long as the participant meets the minimum requirement for urine cotinine levels. Participants who do not meet this requirement will be dismissed from the screening visit without payment. Participants who complete the study will be compensated $120 for the shorter sessions (baseline-session 4) and $135 for the longer sessions (sessions 5-9) and will have a chance to earn an additional $50 bonus for every three sessions that are completed on time as scheduled. There will also be a $100 end of study bonus for a total bonus of $220. If the participant does not attend the screening visit or one of the three weekly visits as scheduled, they will forfeit the bonus. They will have a chance to earn another bonus payment with the next set of three visits. Those who do not complete the entire study will only receive compensation for sessions that they complete.

Quit Attempts During the Study

At each study visit, we will ask the participant if she is currently abstaining from smoking with the intention of quitting. If a participant is currently abstaining from smoking with the intention to quit, we will withdraw her from the study. We will also encourage her to continue abstaining from smoking and provide her with the '*Clearing the Air*' manual and local smoking cessation resources.

Study 1 Randomization

At the end of the baseline session, participants will be randomized into sequences for administration of each of the nicotine conditions for all phases. In Phase 1, subjects will receive one of the three nicotine doses per session (labeled A, B, usual brand), with the doses received in random order, with assignment to one of six possible sequences. In Phase 2 participants will receive two of the three doses at each session. Three doses taken two at a time results in three possible dose combinations (A-B, A-usual brand, B-usual brand). Each subject will receive the paired doses in a random order; there will be six possible sequences to which a subject will be randomly assigned. In Phase 3, subjects will receive the lowest nicotine dose cigarettes paired to the usual brand cigarette. The randomization schedule for Phases 1 and 2 will be based a modification of a Latin Square design. The particular modification is designed to insure that in each Phase: 1) each subject receives each dose/dose pair once, 2) each dose/ dose pair is administered to the same number of subjects in a particular session, and 3) each dose/dose pair follows each other dose/dose pair the same number of times. Randomization for Phase 1 will be performed independent of randomization for Phase 2. In addition, for phases in which subjects receive two doses, the position of the doses (left or right) will be randomly assigned. Participants in each condition will be assigned cigarettes that match their menthol preference. Randomization will be stratified by site and menthol preference.

Condition	TPMF Code	Type*	Specifications Nicotine Yield	Specifications Tar Yield	Specification Range for Nicotine Yield	Specifications Nicotine Content
1	NRC300	RN	0.12 ± 0.03	9 ± 1.5	0.09 - 0.15	2.27 ± 0.08
1	NRC301	RN-Men	0.12 ± 0.03	9 ± 1.5	0.09 - 0.15	0.104 ± 0.002
2	NRC102	RN	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04	0.37 ± 0.01
2	NRC103	RN-Men	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04	0.39 ± 0.00
3	N/A	Usual Brand	N/A	N/A	N/A	N/A
3	N/A	Usual Brand-Men	N/A	N/A	N/A	N/A

*Legend:	
RN	Reduced Nicotine
RN-Men	Reduced Nicotine-Menthol

The lead statistician will create a randomization schedule for each of the two sites, amounting to 150% of expected enrollment at each site. The excess randomization codes will be used in the event that a site will have to enroll extra participants due to unexpectedly slow enrollment at another site. The low-dose nicotine cigarettes will be identified by letter code (A-B) and only Administrative Core personnel with no participant contact will have the link between the statistician's letter code and dose assignments. The usual brand will be identified as such. The randomization schedules and the link between the alphabetic code and treatment assignment will be maintained securely by the Administrative Core. A second, sealed, copy will be secured in a separate building to protect against loss related to fire or other unforeseen events.

The University of Vermont will be responsible for removing all identifying information from cigarettes received from the Research Triangle Institute (RTI), creating kits, labeling each pack with a blind code, assigning product using this blind code based on the randomization schedule being provided by the UVM Biostatistics Core, and shipping cigarette kits to each site as needed based on recruitment. Each site will be responsible for tracking product received and distributed to participants, collecting unused product from participants, and returning unused cigarettes to UVM. The participants, investigators and study staff will not have knowledge of which product is given to a participant or whether different participants received the same or different product.

Study 1 Statistical Methods and Sample Size

Phase 1 data will use repeated measures analysis of variance, within the framework of a cross-over trial with three doses and two times as within-subject factors. In addition, the analysis will include a fixed effect for period (in this case the session) and a random effect to account for sequence. Time by dose interaction will be included in the model to test the primary question of interest, which is if outcomes of interest before and after smoking a cigarette differ by dose. If there are significant dose or time by dose interactions, specific contrasts will be examined to fully describe the nature of the differences, with LSD adjustment for multiple comparisons. Regarding sample size, using the baseline MNWS score observed by Tidey et al. (2012) for another vulnerable population (smokers with schizophrenia), and conservatively using the largest variance found in that study for MNWS, a sample size of 50 completers will provide 84% power to detect a significant difference in time effect between doses if MNWS decreases by 40% for one dose (as was observed in smokers with schizophrenia) and 25% for another dose, using a two-sided type I error rate of 0.05. Power will be 97% to detect a difference in decrease of 40% for one dose and 20% for another. ***Phase 2:*** Repeated measures analysis of variance will be used to compare number of puffs chosen for the three doses and three sessions, with contrasts to determine the relative ordering of dose choices. If the variance across doses is not constant, as was found by Shahan et al. (1999), data will be log-transformed. Regarding sample size, using the largest variance in consumption observed by Shahan et al. (1999), a sample size of 50 completers will provide 89% power to detect a ten puff difference in doses, using a two-sided type I error rate of 0.05. ***Phase 3:*** Repeated measures analysis of variance will be used to compare cross-price elasticity between the lower dose and usual brand cigarettes and prices. Regarding sample size, repeated measures analysis of variance with a 0.05 significance level and an effect size of 0.08 will have 88% power to detect a difference in mean cross-price elasticity between the two dose levels. This assumes a variance of the means of 0.002, a standard deviation at each dose of 0.2 and a between dose correlation of 0.5.

Project 4, Study 2

Study 2 will evaluate the effects of extended exposure to VLNC cigarettes in smokers of childbearing age with < an Associate's Degree. This study will be limited to two conditions: usual brand versus the 0.03 mg dose. After a baseline period in which daily smoking rate and other baseline assessments are completed, participants will be randomly assigned to usual brand or the VLNC condition and followed for 12 weeks. Participants must have technological capabilities to complete weekly face-to-face video assessments and use a smartphone-compatible smokerlyzer for assessing breath carbon monoxide (CO) levels.

Study 2 Screening Procedures

Recruitment:

A sample size of 90 completers is proposed to test the primary aim in Study 2. Anticipating 15% attrition, and five pilot participants (3 at UVM, 2 at the University of Kentucky [UKY]), 111 participants will be enrolled across both sites (74 at UVM, 37 at UKY). Prior to study initiation and participant recruitment, IRB approval will be obtained from the University of Vermont's IRB and University of Kentucky's IRB. Potential participants will respond to community advertisements (local newspapers, community bulletin boards, Facebook, Craigslist, city buses, direct mailers etc.) that contain a study description, link to an

online survey and the name and phone number of the Research Assistant. Direct mailers are mass mailings that are sent to all addresses in a given zip code and are not sent to particular individuals. Mailers will include contact information for the research study so recipients can contact us if they are interested in participating. Potential participants will also be recruited from obstetric practices, WIC offices, and behavioral health programs in Vermont. Pregnant women at these locations will be asked to complete a brief self-administered smoking-screening form containing a multiple-choice question on smoking status that has been validated to enhance accurate reporting (Mullen et al., 1991). This form will be used specifically for research recruitment purposes. Pregnant women who endorse smoking currently will be given the option to sign the smoking-screening form and provide a phone number at which they can be contacted about the study. A study team member will physically collect signed smoking-screening forms to securely transfer them to study offices. Signed forms will be stored in a locked file cabinet in a locked office which participants do not have access to.

Participants can choose to complete the pre-screening questionnaire online or by phone. If deemed eligible, those who complete the online questionnaire will be called by the Research Assistant to further discuss the study. The RA will read a script briefly explaining the study. Participants will be informed that this is not a smoking cessation program, and that smoking cessation services are available in the community independent of their decision to participate in this study. If interested, they will be scheduled for a screening interview.

Those who do not complete the pre-screening questionnaire online will call into the laboratory and be read a script briefly explaining the study. After verbal informed consent is received, the participants will be asked questions over the phone to determine initial eligibility. Callers will be informed that this is not a smoking cessation program, and that smoking cessation services are available in the community independent of their decision to participate in this study.

Potential participants will also be recruited from the UVM Medical Center Comprehensive Obstetric and Gynecologic Services program that cares for pregnant women. Study staff will review electronic medical records (EMR) of pregnant women under the care of Dr. Anne Dougherty, MD, to identify potentially eligible women. Patient name, date of birth, gestational age, and smoking status will be recorded on the pre-screening questionnaire. If patients are not eligible after this limited review of the EMR, the patient will not be contacted. For women who do meet initial eligibility criteria, Dr. Dougherty will first contact the patient to determine if they are interested in the study. Dr. Dougherty will document the patient's interest and notify research staff in the EMR. Study staff will contact the patient using the phone number, mailing address, and/or email address in the EMR. Interested patients will then finish the pre-screening questionnaire over the phone with staff.

All prescreen data, regardless of how it is collected, will be stored separately from study data in REDCap.

Eligible and interested participants will be scheduled for the first portion of the screening interview that will occur over video chat. Research staff will assist participants with setting up an appropriately secure video platform. During this first portion of the screening, the participant will first complete questionnaires through REDCap online while research staff is present over video chat or phone to deliver instructions and to answer any questions. The participant will then answer interviewer-administered questionnaires over video chat. Participants who did not yet set up their video platforms will do so with research staff before beginning any questionnaires. Potential participants will be instructed to show staff identification (example, driver's license) during this screening session. If participants anticipate not having acceptable ID site staff should consult with the project coordinator or study PI.

Research staff may obtain a medical release from participants to confirm pregnancy and gestational age during the first portion of the screening. Participants will be sent a link where they can enter their provider information (provider name, office name, and location) and sign the release electronically. Research staff will contact the participant's provider to obtain confirmation. Alternatively, participants can text or email research staff confirmation of pregnancy and gestational age or show documentation to research staff on camera during either portion of the screening. Confirmation of pregnancy and gestational age must be received before final eligibility is determined.

Participants who are opioid dependent must be maintained on a stable methadone or buprenorphine dose for at least 14 days before participating in the study. Consent to confirm treatment with the participant's maintenance treatment provider will be obtained during the first portion of the screening and confirmation of treatment must be obtained before final eligibility is determined. We will monitor any changes in dose throughout the study. These practices have been effective for confirming clinical stability in our prior smoking trials with opioid-maintained patients.

Participants who meet initial study eligibility during the first screening session will be scheduled for the second portion of the screening. Before the second portion of the screening occurs, eligible participants will receive the equipment necessary to use for collecting physiological measurements. Participants will be asked to pick up this equipment via curbside pickup at our clinic (UVM University Health Center, UHC), which will consist of participants calling staff once they arrive at UHC and staff coming out to give participants a bag/box containing the following equipment: a smokerlyzer; an automated blood pressure cuff; urine cups with attached temperature test strips; a urinary cotinine dipstick; urine toxicology test strips or a saliva toxicology test; and a pregnancy test strip. Participants (and staff) will be asked to use cloth face coverings when exchanging product. Participants may be invited to come inside to pick up this equipment if the participant is asked to wait for this exchange. All participants must pass a COVID19 screening before entering the building. If there is any waiting that needs to occur inside the building, the participant will wait inside one of our five highly ventilated smoking chambers. If there happens to be no space in the smoking chambers, the participant will be told that they can not come up to the clinic until space is available. After each use, the all of the surfaces in the smoking chambers will be cleaned with 70% or greater of alcohol solution by staff wearing a mask and gloves, as well as all of the door handles. If the participant uses the bathroom while they are in the clinic, the bathroom surfaces and handles will be wiped down after use by staff while masks and gloves are worn. Participants who are using the smoking chambers at any point in the study to wait for product or equipment exchange will remain in the chambers until a staff member comes to knock on the door to let them out. In this way, we can avoid people coming into close contact with each other in the larger room that contains the smoking chambers. A minimum of 6 feet of distance will be maintained for all staff and participants at all times. For participants who cannot come to the clinic, a commercial courier will deliver this equipment to them before the second portion of the screening.

If at any point the smartphone-compatible smokerlyzers are not available for distribution, we will use a smokerlyzer stored in our lab to conduct the test curbside before or after participants are invited inside and the courier service will not be available. Research Assistants will bring down the lab smokerlyzer when they bring the rest of the equipment to the participant. While maintaining 10 feet of distance and wearing gloves, staff will explain how the lab smokerlyzer works, including the D-piece (a portable valve filter) that is inserted into the smokerlyzer and the single use plastic mouthpiece that is inserted into the D-piece. The lab smokerlyzer has built in SteriTouch technology to ensure optimum infection control, and the D-pieces filter out 99.9% of airborne bacteria and greater than 97% of viruses for excellent infection control. D-piece technology also includes a one-way valve that prevents air from being drawn back from

the monitor. Each participant will be assigned their own D-piece to use throughout the study, and no D-piece will ever be shared among participants. Once the participant is ready, staff will press the button to obtain the measurement and will set the device down and will back away 10 feet. The participant will then come to pick up the device and will gently blow into it. After the participant completes the test, they will set down the device and back up 10 feet so staff can retrieve it. After every use, staff will wipe down the lab smokerlyzer with disinfectant wipes and hydrogen peroxide wipes. D-pieces will also be wiped down after each use with disinfectant wipes and hydrogen peroxide wipes and stored in a container at the lab.

Once participants have received the necessary equipment to complete the physiological portion of the screening, the research assistant will initiate a video call with the participant. During this call, the participant will be instructed on how to use the equipment and then will be asked to use the equipment to obtain the following physiological readings: breath CO levels, blood pressure, and heart rate. Participants will also be asked to collect a urine or saliva sample during the visit. If a saliva sample is collected, the participant will provide the saliva sample over video while the staff observes. If a urine sample is collected, staff will ask the participant to bring this urine sample to the video screen after collection to perform urinary cotinine, toxicology, and pregnancy tests. The participant will obtain the physiological readings and perform the tests and then will hold the results of the test up to the camera so that staff can interpret and record the readings on REDCap. Participants will also be instructed to have a pack of their usual brand cigarettes and all prescription medications they are currently taking to show to research staff.

A participant must complete her two-part screening session within 30 days of completing the pre-screening questionnaire. If the participant is not able to complete the two-part screening visit in that timeframe, she will need to complete the pre-screening questionnaire again. Participants will be reminded to engage in their normal activities and smoking practices prior to the screening visit.

Informed Consent Process:

Before beginning the informed consent process, potential participants will need to produce identification as described above. The interviewer will confirm the age and identity of the participant. If the participant is not between the ages of 21 and 44, she will be dismissed without payment. During the first portion of the screening session, study information will be presented and documentation of the participant's informed consent via electronic signature on REDCap will be required prior to participating. In order to ensure adequate informed consent, participants will be asked to read the first several lines aloud (to determine literacy) and will then be given ample time to read the consent document. If the interviewer suspects the participant is not literate, he or she will have them continue reading further to confirm. Inability to read and comprehend written study materials will result in ineligibility and the interviewer will inform the participant that they are not eligible. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and her rights as a research participant will the consent form be signed and the participant undergo screening procedures.

Screening Measures

Those who consent will be screened for eligibility using the following measures:

The following physiological measures will be collected and entered directly into REDCap by the interviewer:

1) Expired breath carbon monoxide (CO) levels will be assessed using a smartphone-compatible smokerlyzer (remote collection) or lab smokerlyzer (curbside collection), a reliable and valid measure of recent smoking.
2) Blood pressure and heart rate will be measured using an automated blood pressure monitor to help the licensed medical professional determine final participant eligibility. The research staff will also submit a Medical Event Form for the licensed medical professional to review along with a Blood Pressure and Heart Rate Symptom Checklist to ascertain details of the symptomatology for the licensed medical professional to review. In severe cases, the licensed medical professional may also choose to call the participant to follow-up and/or withdraw the participant from the study if necessary.
3) Urine cotinine will be collected to verify the participant's smoking status. It will be measured using urinary cotinine test strip.
4) A urine or saliva toxicological screen will be performed to assess the presence of the following illicit drugs: marijuana, cocaine, opiates, oxycodone, benzodiazepines, barbiturates, amphetamines, methadone, buprenorphine, methamphetamines, MDMA and PCP. Participants who fail the drug screen for drugs other than marijuana, prescribed opioid medication, or other medications as determined by the PI on a case-by-case basis may reschedule the interview but will need to be re-consented to ensure they have received adequate informed consent. They will be excluded if they are positive for drugs (other than marijuana, prescribed opioid medication, or other medications as determined by the PI on a case-by-case basis) the second time.
5) Urine pregnancy test (HCG detection) will be performed for all participants to confirm pregnancy.

The following screening assessments will be administered as an interview and then will be entered into REDCap by the interviewer at the end of the visit:

1) The Mini International Neuropsychiatric Interview (MINI 7.0) (Sheehan et al., 1990) a structured diagnostic interview to evaluate psychiatric disorders.

The following screening assessments will be administered as an interview and entered directly into REDCap by the interviewer:

1) MINI PLUS 7.0 Modules
2) MINI suicide subscale (Sheehan et al., 1997) to evaluate suicide risk.
3) Tobacco Use History and Exposure Questionnaire, which measures variables such as smoking amount, cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking.
4) Smoking Cessation Therapy Use Questionnaire
5) Time Since Last Cigarette Questionnaire-Screening
6) Timeline Follow Back - Screening
7) Medical History Questionnaire to assess current diagnoses, symptoms and past health problems.
    a. Medications will be recorded directly onto the Concomitant Medications Form in REDCap
8) MINI Follow-up Questionnaire (if applicable)
9) Maintenance Drug Dose Questionnaire – Screening Version, if participant reports opioid maintenance

The following screening assessments will be completed by the participant directly in REDCap, except where noted otherwise:

1) Demographic History Questionnaire, which will assess age, ethnicity, race, education, income, marital status, and employment history.
2) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991)
3) Wisconsin Inventory of Smoking Dependence Motives-brief Scale (WISDM-brief; Piper et al., 2008), will be administered to assess nicotine dependence severity.
4) Smoking Stages of Change Algorithm as well as a contemplation ladder to assess intention to quit smoking (DiClemente et al., 1991).
5) Identifying Information Form will include the participant's REDCap Subject Identifier, name, address (including the county of residence), email address, phone number, age, date of birth, and social security number (if applicable).
    a. This form will be entered into the 'Identifying Information Access Database'.
        i. Each site will have a separate 'Identifying Information Access Database'.
        ii. Identifying information will not be shared with other sites. Each site is responsible for maintaining confidentiality of this information.
        iii. Identifying information will be kept in a locked file cabinet (source document) and in a password protected Access Database (electronic version) separate from all other study data.
6) Beck Depression Inventory (BDI-II; Beck, Ward, & Mendelson, 1961), to assess depressive symptoms.
7) Overall Anxiety Severity and Impairment Scale (OASIS; Norman et al., 2006) to assess frequency and severity of anxiety symptoms.
8) COVID-19 Symptom Questionnaire

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be record securely by research staff. The interviewer will enter the data into REDCap when it resumes functioning properly. A note indicating that REDCap was not functioning during the session should be recorded in the 'End of Visit Evaluation Form'.

Suicidality/Mental Health Monitoring

Participants who endorse suicidal intention in the past month or a suicide attempt in the past 6 months as indicated on the BDI (score > 1 on question 9) or MINI suicide subscale (endorse question 4 and/or 5 on the MINI suicide subscale or question 6 on the MINI suicide subscale with suicide attempt in the past 6 months) or answer "yes" to question A3g on the MINI Neuropsychiatric Interview and symptoms have occurred in the past two weeks will be assessed by research staff for eligibility and possible intervention. The staff member will contact a licensed clinician for evaluation. In the event that no clinician is available, staff will put the participant in contact with the National Suicide Prevention Lifeline at 1-800-273-8255. They will also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible. Additionally, they will contact the Project Coordinator to inform her of the situation. The participant will be paid $25 and provided with local mental health resources. Post enrollment, any report of suicidal intent or attempt by a participant will be grounds for immediate withdrawal from the study.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Pregnant women ages 21-44 years who have < an Associate's Degree
2) Have appropriate equipment to complete face-to-face video assessments. For participants who do not have smartphone, research staff will explore potential alternative plans (e.g., provide inexpensive Android phone)
3) Have a positive urine cotinine dipstick
4) Be without current (within the past year) serious mental disorder that would interfere with study results or completion as determined by the licensed medical professional or PI
5) Be sufficiently literate to complete the research-related tasks
6) Be in good physical health without serious illness or change in health or medication in the past three months as determined by the licensed medical professional
7) Report no significant use of other tobacco or nicotine products within the past month (more than 9 days in the past 30)
8) Provide verification of gestational age ≤ 25 weeks from OB/GYN at time of enrollment

Eligibility based on inclusion criteria #1 and 2 above will be determined after the first portion of the screening. Eligibility based on criteria #3-7 will be determined after the second portion of the screening. Criteria #8 may be determined during the first or second portions of the screening if the participant has documentation of gestational age available to send to research staff. If the participant does not have documentation available, she will provide authorization for research staff to contact her provider to obtain confirmation.

Exclusion Criteria:

1) Exclusive use of roll-your-own cigarettes
2) Planning to quit smoking in the next 30 days
3) A quit attempt in the past 30 days resulting in greater than 3 days of abstinence
4) Currently taking anticonvulsant medications including:
    a. Phenytoin [Brand Name: Dilantin]
    b. Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]
    c. Oxcarbazepine [Brand Name: Trileptal]
    d. Primidone [Brand Name: Mysoline]
    e. Phenobarbital
5) Currently seeking treatment for smoking cessation
6) Have used nicotine replacement, bupropion or other pharmacotherapies as cessation aids in the past month
7) Current symptoms of psychosis, dementia, or mania
8) Suicidal ideation in the past month (score > 1 on the BDI question 9 or endorse question 4 and/or 5 on the MINI suicide subscale)
9) Reporting a plan or attempt to commit suicide, which is assessed on question A3g of the MINI Neuropsychiatric Interview Major Depressive Episode Module. Thoughts of suicide without an intent or plan is not an exclusion criteria
10) Suicide attempt in past 6 months (endorse question 6 on the MINI suicide subscale with suicide attempt in the past 6 months)
11) Participation in another research study in the past 30 days

12) Reporting symptoms of COVID-19
13) Positive toxicology screen for any of the following drugs will be grounds for exclusion: cocaine, opiates, methadone, oxycodone, buprenorphine, benzodiazepines, barbiturates, amphetamines, methamphetamines, MDMA and PCP.
    a. Marijuana will be tested for but will not be an exclusionary criterion. Participants will be discouraged from smoking marijuana during the study.
    b. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, or amphetamines will not necessarily be excluded.
    c. Participants failing the toxicology screen will be allowed to re-screen once, if they are still eligible for the screening at the time of the re-screen. These participants will need to be re-consented before being rescreened to ensure they have received adequate informed consent.
14) Systolic blood pressure < 80 or ≥ 140 mmHg
    a. Participants failing for blood pressure will be allowed to re-screen once.
15) Diastolic blood pressure < 50 or ≥ 90 mmHg
    a. Participants failing for blood pressure will be allowed to re-screen once.
16) Breath CO > 50 ppm
17) Heart rate is greater than or equal to 110 bpm or less than 45 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.

Eligibility based on exclusion criteria #1-12 above will be determined after the first portion of the screening. Eligibility based on criteria #13-17 will be determined after the second portion of the screening.

Women under age 21 are excluded because they cannot legally buy cigarettes. Those with unstable medical, psychiatric, or medication conditions (condition and/or medication changes in the past three months) are excluded as these symptoms could affect a participant's ability to complete the study. Examples include but are not limited to the following: angina, stroke, heart attack which occurred since phone screening, blood clots in the arms or legs for which the individual is undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy, 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. Individuals with baseline CO readings greater than 50 ppm, those with blood pressure or heart rate readings that are out of range (acceptable ranges are systolic: 80-139 mmHg; diastolic: 50-89 mmHg; heart rate: 45-109 bpm) and anyone who has attempted suicide in the past 6 months will be excluded from the study for safety concerns. Individuals who smoke 'roll your own' cigarettes exclusively will be excluded from the study because we will be unable to standardize their baseline smoking behavior. Individuals who have recently participated in a research study will be excluded as participation may have changed their smoking behavior, which may preclude a stable smoking baseline. Because participants are required to complete portions of the protocol independently, they will need to be able to independently read and comprehend the study materials.

Eligibility Determination:
The research assistant will review the entire screening assessment battery for initial eligibility determination, confirming the subject meets the above described inclusion/exclusion criteria. The final eligibility of the participant will be determined by a licensed medical professional (MD, DO, NP, PA, Master's prepared RN or CRN) at each site after reviewing the Medical History Questionnaire, BDI, Mini Neuropsychiatric Interview, and the MINI suicide subscale. The licensed medical professional may meet with a participant if available and think it necessary for eligibility determination. He/she will sign off on

eligibility prior to the first baseline visit. If the licensed medical professional determines the participant is not medically eligible to participate in the study, has current symptomatology that would interfere with interpretation of the data or is unlikely to complete the study he/she will inform the research assistants who will contact the participant prior to the first baseline visit. The licensed medical professional will not need to review the medical history forms of participants who are not eligible for other, non-medical reasons.

If a participant fails the urine or saliva toxicology screen due to a prescription medication she is taking, then she will not be automatically excluded. The interviewer will make note of this when he/she submits the forms to the licensed medical professional for final eligibility determination.

Once all the screening procedures have been completed, researchers will pay participants $25 for their time as long as they meet the requirements for urine cotinine. Participants will be paid after the completion of the study visit. If participants are deemed ineligible at any point in the screening, the participant will be paid after they are determined ineligible. Participants who meet all other eligibility criteria, sans the medical criteria, will be scheduled for the first baseline visit.

At the end of the screening session, the researcher will complete the End of Visit Evaluation Form. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regards to self-report of tobacco use.

Study 2 Baseline Procedures

This study will use a one-week, two-session baseline period to collect baseline individual difference measures and monitor daily usual-brand smoking behavior. During the baseline period, participants will not be provided their usual brand cigarettes to smoke. Use of a two session baseline period will ensure stability of daily smoking reports, reduce reactivity to the daily cigarette monitoring, and reduce participant burden. During the two baseline sessions, participants will complete subjective questionnaires. Each visit will last approximately two hours or less. At the end of each baseline session, the researcher will complete the End of Visit Evaluation Form. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regards to self-report of tobacco use.

Participants will also be supplied with urine collection equipment either by curbside pick-up or courier service at time of Screening or Baseline 1 assessment so that they can collect first void urine samples during the Baseline 2 visit.

For the Baseline 1 visit and all subsequent visits, the participant will be sent a REDCap link within 15 minutes of the start of the scheduled visit to complete all of the non-interviewer administered questionnaires. The participant will complete these questionnaires on their own but can have the research staff member present on a video call if they desire. Before beginning the physiological assessment portion of the visit over video call, research staff must review the participant's questionnaire responses for that visit. Participants will be compensated after the completion of the study visit and when the participant has received their new product.

At Baseline 2 and all subsequent visits, after the participant has answered the questionnaires and has completed the physiological portion of the visit over video call, they will be asked to come to the lab for exchange of product and biological samples. Participants will bring in their used and unused product from

the previous visit (starting at Week 1). Additionally, first-void urine samples will be collected at Baseline 2, Week 6, and Week 12 for assessing tobacco-related toxin exposure. Participants will be instructed to call staff at the office when they get to the clinic to ensure that there is enough space in the smoking chambers to house all participants while abiding by safety guidelines as detailed on page 14 of the protocol. All participants must pass a COVID19 screening before entering the building. When invited into the lab, the participant will be shown to a smoking chamber and will instructed to place their bag of product outside of the chamber. The participant will wait here while the staff processes and returns product through the randomization database. Staff will dispense new product and bring the bag back to the participant. When the RA deems it safe for the participant to exit the chamber, the RA will instruct the participant that they can leave. The RA will instruct the participant to observe social distancing measures during this exchange, providing clarification if necessary. If a participant forgets their first-void urine sample at the Baseline 2 visit, staff will ask participant to come back to the clinic with their first void urine sample before exchange of product occurs. If participant is unable to return to the clinic with their first void sample, staff can arrange to meet the participant off campus to pick up their urine sample and to give participant their study product. Distancing and safety measures as described above must be observed. For participants who cannot make it to UHC, special arrangements will be made to enable use of the randomization database and product return/distribution procedures to the extent possible. Each week, during - or scheduled as nearly as possible to – a virtual visit, a complete accounting of the participant's product inventory will be taken and processed remotely through the randomization database. The participant will separate product based on its status (used/unused), and staff will process return characteristics through the database accordingly. Staff will clarify barcode characteristics with the participant when legibility is compromised. When the exchange is done via courier, the participant will be instructed to keep unused product in their possession, but to exchange any used product with the courier who will deliver newly dispensed replacement products within 48 hours.

Product that will be given to participants for the Baseline 2 visit cannot be given/sent to participants until 7 days have passed following completion of the Baseline 1 visit. We will need to calculate baseline smoking rate during this 7-day period and so participants cannot have access to any study product before this 7-day period has ended.

Visit scheduling requirements for baseline period:

Participants will be required to schedule the Baseline 1 visit within 30 days of the completion of their screening visit. If a participant still wants to be in the study after 30 days, she will need to be re-screened. The participant will need to be re-consented but will maintain the original REDCap Subject Identifier. The ideal target window separating Baseline 1 and Baseline 2 is between 7 and 12 days. The minimum is 7 days and the maximum is 21 days. If the participant does not complete the visit within 21 days, then she will not be rescheduled and will be discontinued from the study.

Measures/Assessments

The following physiological measures will be collected at Baseline 1 and recorded directly into REDCap by the interviewer:

1) CO
2) Blood pressure
3) Heart rate

The following assessments will be administered as an interview at Baseline 1 and entered directly into REDCap by the interviewer:

1) Concomitant Medications Form
2) Time Since Last Cigarette Questionnaire
3) Health Changes Questionnaire, which will assess any weekly health changes
4) Maintenance Drug Dose Questionnaire (if applicable)

The following assessments will be administered at Baseline 1 and completed by the participant directly in REDCap:

1) BDI
2) OASIS
3) Perceived Health Risks Rating (Hatsukami et al., 2010), a measure of the perceived addictive potential and other health risks associated with cigarettes
4) Respiratory Health Questionnaire, a measure of cough, shortness of breath and other respiratory symptoms
5) Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986), a measure of nicotine withdrawal
6) Questionnaire of Smoking Urges-brief scale - Usual Cigarette (QSU-brief; Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991), which measures the urge to smoke
7) Cigarette Evaluation Scale – Usual Cigarette (CES; Westman, Levin, & Rose, 1992), which measures responses to cigarettes (e.g., reward, satisfaction)
8) Intolerance for Discomfort Questionnaire (IDQ; Sirota et al., 2013), assesses intolerance for the discomfort of smoking abstinence. The measure includes three subscales: physical discomfort, emotional discomfort and smoking withdrawal discomfort.
9) Cigarette Purchase Task - Usual Brand Version (CPT; MacKillop et al., 2008), a self-report analogue of a progressive-ratio schedule that measures the relative reinforcing efficacy of cigarettes by querying how many of that day's cigarette they would consume in a day at varying prices. This task will indicate whether prolonged VLNC cigarette use reduces cigarette demand and increases sensitivity to increases in cigarette costs.
10) Perceived Stress Scale - 4 item (PSS-4; Cohen, Kamarck, & Mermelstein, 1983), which measures the degree to which life situations are appraised as stressful
11) Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegan, 1988), which measures symptoms of positive and negative affect
12) Pregnancy-Unique Quantification of Emesis Scale – 24 hour (PUQE-24; Ebrahimi et al., 2009), which assesses severity of nausea and vomiting specific to pregnancy.
13) COVID-19 Symptom Questionnaire

The following Baseline 2 physiological measures will be collected and recorded directly into REDCap by the interviewer:

1) CO
2) Blood pressure
3) Heart rate

The following assessments will be administered as an interview at Baseline 2 and then entered directly into REDCap by the interviewer:

1) Concomitant Medications Form
2) Time Since Last Cigarette Questionnaire
3) Health Changes Questionnaire
4) Maintenance Drug Dose Questionnaire (if applicable)

The following assessments will be administered at Baseline 2 and completed by the participant directly in REDCap:

1) BDI
2) OASIS
3) FTND
4) WISDM-brief
5) PUQE-24
6) COVID-19 Symptom Questionnaire

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be recorded securely. The interviewer will enter the data into REDCap when it resumes functioning properly. A note indicating that REDCap was not functioning during the session should be recorded in the 'End of Visit Evaluation Form'.

Interactive Voice Response System:

At the end of the first baseline visit, participants will be trained to use the Interactive Voice Response (IVR) System, which will contact participants each day throughout the study and ask about their smoking behavior as well as withdrawal symptoms the week before and after randomization. We will also review the IVR adherence incentive program, which consists of $1 per call plus a $10 bonus for seven consecutive calls. Participants may be provided a study cell phone if they have unreliable telephone access, do not have enough monthly cell phone minutes or prefer not to use their own phone.

The IVR system is operated by TeleSage. To be enrolled in the IVR system, research staff will enter the participant's initials, telephone number, subject identifier, and visit dates into the IVR TCORS website. Identifying information (initials and telephone numbers) will not be extracted with the data by the bioinformatics group. Please refer to TeleSage's privacy statement and HIPAA compliance form for additional information.

Baseline 2 biological specimens:

1) <u>Urine sample for smoking biomarker assessment</u>**:**
   Participants will be asked to provide a urine sample (first void of the day) at the second baseline session for biomarker assessment. Samples will be stored at temperatures no more than -80°C. The tobacco-specific carcinogen biomarkers are total NNAL and PAH. Total cotinine levels will also be assessed to measure daily nicotine exposure. Participants will be reminded with a phone call the day before the visit, those who forget will be asked to return to the lab with their first void

urine sample or staff can arrange to meet the participant off campus to pick up their urine sample.
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Biomarker shipping and storage:
Biomarkers will be shipped quarterly to the University of Vermont Laboratory for Clinical Biochemistry Research (Tracy Lab). The Tracy Lab will serve as a central repository for all biomarker specimens and will be responsible for distributing specimens to the appropriate labs on a quarterly basis. Urine samples will be analyzed and stored at the University of Minnesota Hecht Lab.

Study 2 Experimental Procedures

Experimental Period:
Participants will be seen weekly throughout the 12-week experimental period. Study Weeks 2, 6, and 12 will take approximately 2-4 hours each. All other sessions will last 1-2 hours. As a part of each experimental visit, participants will be asked to come to UHC for a product exchange. All participants must pass a COVID19 screening before entering the building. Participants will be instructed to contact the RA at the office when they get to the clinic to ensure that there is enough space in the smoking chambers to house all participants while abiding by safety guidelines as detailed on page 14 of the protocol. When invited into the lab, the participant will be shown to a smoking chamber and will instructed to place their bag of product outside of the chamber. The participant will wait here while the RA processes and returns product through the randomization database. Then the RA will dispense new product and bring the bag back to the participant's smoking chamber and leave it on the ground in front of the chamber. When the RA deems it safe for the participant to exit the chamber, the RA will instruct the participant that they can leave. The RA will instruct the participant to observe social distancing measures during this exchange, providing clarification if necessary.

Visit scheduling requirements for experimental period:
The ideal scheduling window between each visit is 7 days based on the date of the Baseline 2 (randomization) Visit. For additional scheduling requirements, refer to the '*Scheduling Visits SOP*'. If a participant misses a visit and is not able to reschedule during the window (± 3 days), that visit will not be 'made-up' in the future. All measures that were not completed will be considered missing data and will not be collected during future visits. If a visit mistakenly occurs outside of the designated window, this is a protocol deviation. A 'Non-Medical Event Form' will need to be completed. Additionally, each visit should occur at approximately the same time of day ± 1 hours.

If a participant is not able to attend her Week 12 visit, then it should be rescheduled even if it is outside of the scheduling window. This will be documented as a protocol deviation.

<u>Experimental Visits: Study Weeks 1, 3, 5, 7, 9, and 11</u>:

Measures/Assessments

Physiological Measures will be collected and entered directly into REDCap by the interviewer:

1) CO
2) Blood pressure
3) Heart rate

The following assessments will be administered as an interview and will be entered directly into REDCap by the interviewer:

1) Concomitant Medications Form
2) Time Since Last Cigarette Questionnaire
3) Health Changes Questionnaire
4) Medical Event Form (if applicable)
5) Maintenance Drug Dose Questionnaire (if applicable)

The following assessments will be completed by the participant directly in REDCap:

1) BDI
2) OASIS
3) MNWS
4) QSU brief – with reference to assigned cigarette
5) CES – with reference to assigned cigarette
6) PUQE-24
7) COVID-19 Symptom Questionnaire

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be recorded securely. The interviewer will enter the data into REDCap when it resumes functioning properly. A note indicating that REDCap was not functioning during the session should be recorded in the 'End of Visit Evaluation Form'.

Experimental Visits: Study Weeks 2, 4, 6, 8, 10 & 12:

Measures/Assessments

Physiological measures will be collected and entered directly into REDCap by interviewer:

1) CO
2) Blood pressure
3) Heart rate

The following assessments will be administered as an interview and will be directly entered into REDCap by the interviewer:

1) Concomitant Medications Form
2) Time Since Last Cigarette Questionnaire
3) Health Changes Questionnaire
4) Medical Event Form (if applicable)
5) Maintenance Drug Dose Questionnaire (if applicable)

The following assessments will be completed by the participant directly in REDCap:

1. BDI
2. OASIS
3. FTND
4. WISDM-brief
5. PSS-4
6. PANAS
7. PUQE-24
8. COVID-19 Symptom Questionnaire
9. Respiratory Health Questionnaire (Study Weeks 2, 6, and 12 only)
10. Perceived Health Risks Questionnaire (Study Weeks 2, 6, and 12 only)
11. CPT – with reference to assigned cigarette (Study Weeks 2, 6, and 12 only)
12. Smoking Stages of Change Algorithm and Contemplation Ladder (Week 12 only)

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be recorded securely. The interviewer will enter the data into REDCap when it resumes functioning properly. A note indicating that REDCap was not functioning during the session should be recorded in the 'End of Visit Evaluation Form'.

Biological Samples to be collected (Study Weeks 6 and 12 only):

1) First void urine sample

Interactive Voice Response System:

Participants will continue to use the IVR system on a daily basis throughout the experimental period to record the number of study cigarettes smoked per day and use of non-study cigarettes, if applicable. During the first week after Baseline 2 (randomization), the IVR system will collect information about withdrawal symptoms.

Variable Incentive Program:

An incentive program has been developed with the goal of improving attendance at scheduled assessment sessions and encouraging honest self-reports regarding all nicotine/tobacco use.

Briefly, participants will receive a total of five tickets for each visit they attend after randomization. Participants will be instructed that these tickets correspond to attendance (three tickets) and honest reporting (two tickets). They will be further instructed that these tickets "could" be eligible for entry into a monthly drawing for prizes, but that only tickets that are "validated" will be eligible for prizes.

Since it is prohibitively expensive to test urine samples each week for each participant and because it is currently not feasible to detect with reasonable precision non-compliance based on biomarkers in the higher nicotine group, we plan to only validate the attendance tickets. Hence, each participant who attends their regularly scheduled weekly session will have a total of five validated tickets entered into the monthly drawing.

To convey the message that we may be validating honest reporting and use of only study-provided products, in a bogus pipeline of sorts, we will tell the participants that a composite assessment of the measures that we collect MAY be used to validate the amount of nicotine and tobacco products that they are using. So there is some minor deception involved, but technically we could conduct urine

toxicology testing for both purposes. Hence, if the urine toxicology testing is presented as something that MAY be done for validation purposes, we feel that any deception is relatively minor. For scientific/economic reasons we are just electing to restrict validation to attendance. Nevertheless, we will debrief all participants upon the completion of the trial. We will inform them that the incentive program was based exclusively on attendance due to the relatively high cost of urine toxicology testing and other practical problems with shipping the urines for prompt testing.

Drawings will be conducted on the 1st of each month. Validation will be performed by staff who have no participant interaction and are not blind to condition. Any ticket drawn will be eligible for an incentive as the only true contingency is for attendance. There will be no mention of the basis for earning incentives (i.e., whether the ticket was for attendance, honesty, adherence,). Participants will simply be informed that he or she earned an incentive from the drawing.

Each drawing will be independent (without replacement); consequently, some participants will not win a prize and others may win more than one during the study if more than one of their tickets is drawn. After confirming winners, the remaining tickets from each month will be discarded (i.e., tickets will only be entered into one drawing). The monthly prize amounts are detailed below.

Grand Prize (1): $500 cash
Second Prize (1): $200 cash
Third Prize (5): $10 cash

Product and Procedures Compliance Review Sessions:

At each visit, Baseline 2 through Week 12, participants will be counseled about their use of the study cigarettes, if applicable. Participants will be asked about any concerns or obstacles associated with use of the study cigarettes. The importance of honest self-reporting will be stressed. Participants will be told that they will not be penalized for use of other nicotine or tobacco products and that it is crucial for them to report any use of these products. 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 IVR completion, visit attendance, task engagement and product accountability. Refer to the '*Product and Procedures Compliance Review Sessions SOP*' for more information.

Quit Attempts During the Study:

At each study visit, we will ask the participant if she is currently abstaining from smoking with the intention of quitting. Although this study is not a treatment program, if a subject quits smoking they will still able to participate. Subjects who quit smoking may continue to be enrolled in the study and receive compensation even if they are not smoking, as long as they continue study visits and regular monitoring. We will provide subjects endorsing a quit attempt with information about smoking cessation and referrals to local treatment programs. We will also give subjects the option of taking study cigarettes home. Subjects will be under no obligation to smoke these cigarettes, but will still be required to keep track of them, and bring them to the laboratory each visit.

If a Participant is Currently Abstaining from Smoking with the Intention to Quit:

- Encourage participant to continue abstaining from smoking
- Schedule the participant for normal weekly visits.
- Provide the participant with the '*Clearing the Air*' manual and local smoking cessation resources
- Give the participant the option to receive study product rather than require her to take the product
- If the participant chooses to receive the study product have her sign a form acknowledging that cigarette availability could be detrimental to the quit attempt. Recommend that she put the product "away" at home as to avoid unwanted cues to smoke.
- If the participant chooses not to receive the study product, have her contact the lab if she lapses and would like to pick up or be mailed the study product prior to her next visit.

If a Participant is Planning to Quit Smoking, but has not initiated the quit attempt:

- Ask if she has identified a target quit date and, if so, what that target date is
- Provide the participant with the '*Clearing the Air*' manual and local smoking cessation resources
- Provide the participant with the study product as usual. Recommend that on the target date she put the product "away" at home as to avoid unwanted cues to smoke.

Abstinence Assessment Session:

After the week 12 visit, participants will be required to attend one additional visit the following day. Participants will have been encouraged to abstain from smoking leading up to this visit . The abstinence assessment session should be scheduled no less than 18 hours and no more than 30 hours after the Week 12 visit. Abstinence will be verified by CO levels that have decreased by at least 50% from the measure taken during the Week 12 visit. This session will allow us to determine whether the experimental cigarettes have reduced the effects of abstinence on these measures relative to the control conditions. If the participant does NOT meet abstinence criteria, she will only receive $20 for the visit.

Measures/Assessments

Physiological measures will be collected and entered into REDCap by the interviewer:

1) CO
2) Blood pressure
3) Heart rate

The following assessments will be administered as an interview and will be entered directly into REDCap by the interviewer:

1) Concomitant Medications Form
2) Health Changes Questionnaire
3) Time Since Last Cigarette Questionnaire
4) Medical Event Form (if applicable)
5) Maintenance Drug Dose Questionnaire (if applicable)

The following assessments will be completed by the participant directly in REDCap:

1) BDI
2) OASIS
3) MNWS
4) QSU-brief – with reference to assigned cigarette
5) CPT - with reference to assigned cigarette
6) CES – Usual Brand Cigarette Version
7) COVID-19 Symptom Questionnaire

In the event that the REDCap website is not functioning, the assessments will be administered aloud and participant answers will be recorded securely. The interviewer will enter the data into REDCap when it resumes functioning properly. A note indicating that REDCap was not functioning during the session should be recorded in the 'End of Visit Evaluation Form'.

Participants who do <u>NOT meet</u> abstinence criteria will be required to complete the following assessments:

1) CO
2) Blood pressure
3) Heart rate
4) Concomitant Medications Form
5) Health Changes Questionnaire
6) TLFB
7) Medical Event Form (if applicable)
8) BDI
9) OASIS
10) COVID-19 Symptom Questionnaire

Gestational Week 28 Phone Call

Participants who have completed the study prior to week 28 of gestation will have a follow-up phone call at approximately 28-weeks gestation. Researchers will collect smoking patterns in the non-intervention period between completion of the study and giving birth by administering a Timeline Follow Back, which will assess tobacco and nicotine product use during the past 7 days. Participants will be compensated $25 for completion of this call.

Participant Compensation:

The total amount of money that participants could earn for this study is $2346 . Participants will receive $25 for completing the screening visit, plus an additional $25 bonus for completing the visit on time as scheduled. Payment will be made regardless of enrollment as long as the participant meets the minimum requirements for CO or urinary cotinine levels. Participants will receive $100 for each of the shorter sessions (Baseline 1, Study Weeks 1, 2, 3, 4, 5, 7, 8, 9, 10, and 11), $150 for each of the longer sessions (Baseline 2, Weeks 6 & 12), $40 for biochemical verification of abstinence, $25 for completion of Gestational Week 28 phone call, up to $221 for completing daily IVR reports of study cigarette and other nicotine and tobacco use. Participants will also have a chance to earn an additional $50 bonus for

every three visits that are completed on time as scheduled. There will also be a $100 bonus for completing the study for a total bonus of $325. If the participant does not attend the screening visit or one of the weekly visits as scheduled, they will forfeit the bonus. They will have a chance to earn another bonus payment with the next set of three visits. Participants will also have a chance to earn additional money through the Variable Incentive Program. As mentioned above, participants will have a chance to earn additional incentives each month for compliance, honesty and attendance. Participants will be given a debit card at the beginning of the study (during the second portion of the screening visit) and compensation for each visit will be automatically transferred to the card after they complete that visit. If debit cards are unavailable, participants will be paid via an alternate method (i.e. cash or check).

End of Study:

After a participant has completed all study procedures and has been paid for participation the research assistant will read the following script and give the participant the *Clearing the Air Manual.*

"If you've reduced your smoking during this study, we encourage you to continue these reductions or even consider quitting. We would like to provide you with some resources should you decide to try to abstain from smoking (give "Clearing the Air" and hotline information). Please also feel free to consult with your physician and use any medications she deems appropriate. We will call you in approximately 30 days to ask about your smoking since leaving the study. There is no right answer and we know how difficult quitting can be. Please just answer honestly. The call will take less than 5 minutes. Thanks again for your participation."

The following assessments will be administered using REDCap:

1) End of Study Questionnaire

30 Day Follow up Phone Call:

Participants will receive a follow-up phone call between 25 and 35 days after the abstinence assessment session to assess their smoking patterns. The phone questionnaire will last less than five minutes. The questionnaire will ask if the participant is still smoking, how much and whether she has attempted to quit smoking since the end of the study. Participants will receive 5 variable incentive program lottery tickets for completing the call as compensation. Those who report abstinence will be invited to complete for biochemical verification and be compensated $40 for doing so. A urine sample will be collected to test urine cotinine levels. Additionally, any Medical Event Forms that remain open from the last session will be discussed.

Once a participant has completed all study procedures and all open events have been closed, the PI or project manager will review the participant's records and sign a form indicating study completion for that participant.

Birth Outcomes Data

Researchers will collect birth outcome data through review of maternal birth medical records.

Study 2 Randomization

At the end of the Baseline 2 session, participants will be randomized into one of two cigarette conditions. Participants in each condition will be assigned cigarettes that match their menthol preference. Participants will be randomized, using block randomization, in equal number to the dose conditions, with randomization stratified by study site and menthol status. Each site will randomize participants until the total goal of 106 participants across both sites is reached, and no effort will be made to recruit a specific number of menthol and non-menthol smokers at each site.

Condition	TPMF Code	Type*	Specifications Nicotine Yield	Specifications Tar Yield	Specification Range for Nicotine Yield	Specifications Nicotine Content
2	NRC102	RN	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04	0.37 ± 0.01
2	NRC103	RN-Men	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04	0.39 ± 0.00
3	N/A	Usual Brand	N/A	N/A	N/A	N/A
3	N/A	Usual Brand-Men	N/A	N/A	N/A	N/A

*Legend:	
RN	Reduced Nicotine
RN-Men	Reduced Nicotine-Menthol

The lead statistician will create a randomization schedule for each of the two sites, amounting to 150% of expected enrollment at each site. The excess randomization codes will be used in the event that a site will have to enroll extra participants due to unexpectedly slow enrollment at another site.

The University of Vermont will be responsible for assigning product based on the randomization schedule being provided by the UVM Biostatistics Core, and shipping the study cigarettes to each site as needed based on recruitment. Usual brand cigarettes will be purchased by each site as needed. Each site will be responsible for tracking product received and distributed to participants, collecting unused product from participants, and returning unused VLNC cigarettes to UVM.

During weeks 1-12, participants will be provided with a 10-day supply of research cigarettes equivalent to 100% of their smoking rate. This will ensure adequate availability of cigarettes in the numerous locations participants may typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if they miss a scheduled visit. Participants will be instructed to use the research cigarettes through Week 12, at which point they are to discontinue product use.

If there is prior knowledge a participant will be missing a visit (i.e. planned vacation, laboratory closure, etc.), then the participant will be provided with an adequate supply of cigarettes to make up for the missed visit(s).

Participants will be asked to refrain from use of other non-study cigarettes during the study period. However, they will be told there is not a penalty for use of non-study cigarettes, and that it is crucial for them to report any use of non-study cigarettes or other nicotine or tobacco products. Throughout the baseline and experimental periods, an Interactive Voice Response (IVR) system will be used on a daily basis to record the number of study cigarettes and non-study cigarettes used the previous day. During the baseline and first experimental week, participants will also answer daily IVR questions about their mood. Participants will be seen weekly for assessments. Brief standardized review sessions focusing on compliance with the study cigarettes and other study procedures will be provided at each visit.

Product Accountability:

Participants will be required to keep track of all the cigarettes provided to them. Therefore, they will be instructed to return all unused cigarettes and empty cigarette packs to the laboratory each week. Research staff will complete the 'Product Accountability Log' as they process participants' products. Any discrepancies in the product dispensed versus product returned will be discussed and recorded in the log. Empty cigarette packs will not be saved; however, research staff will keep all empty cartons in storage for reference. Unused cigarettes will be re-distributed to the participants during Weeks 1-12. Any remaining unused cigarettes returned by the participants will be collected by the research staff.

If participants lose more than two packs of cigarettes and require an unscheduled visit to the laboratory to supplement their supply, they will be told the next time they lose more than two packs they will have to wait until their next scheduled appointment to receive more cigarettes.

Study 2 Statistical Methods and Sample Size

Continuous outcomes will be summarized by the mean, standard deviation, median and range. Categorical outcomes will be summarized by frequencies and percentages. Skewed continuous outcomes will be log- or square-root transformed as appropriate. Variables measured at each baseline visit will be averaged and the average will be used as the baseline measurement. As we expect conditions will be balanced on important baseline characteristics due to randomization, our primary analysis for all endpoints will not be adjusted for potential confounders. However, a secondary analysis will be completed for all outcomes adjusting for demographic characteristics (e.g., age) that we found to be important in prior studies. Potential moderators such as obesity (BMI above or below 30) will be explored by adding that term to the model and the moderator-by-condition term to the model.

The Primary Aim of Study 2 is to compare the effects of cigarettes varying in nicotine yield on smoking rate. The primary endpoint is cigarettes per day (CPD) at 12 weeks. CPD will be collected by daily IVR and/or TLFB at each session to assess cigarette use in the days since the last interview. This will yield a continuous record of cigarette use throughout the study. A weekly average will be obtained for analysis by averaging CPD from the previous visit to the current visit. Additional measures addressing this aim are breath CO level, urinary cotinine concentration, and nicotine dependence (FTND, WISDM) scores. Secondary Aim 1 is to assess adherence to assigned tobacco products and use of multiple nicotine

products during extended exposure. Secondary Aim 2 is to quantify the effects of VLNC cigarettes on (a) biomarkers of exposure to tobacco carcinogens (urine total cotinine, NNAL, PAH)s.

To examine these Aims, repeated measures analysis of variance (ANOVA) will be used for outcomes that are measured repeatedly from baseline to the end of the treatment phase. Each repeated measures ANOVA model consists of five terms: cigarette condition effect, visit effect, interaction effect between cigarette condition and visit, random subject effect (between-subject error), and random error (within-subject error). The variance-covariance structure will be specified as the first-order autoregressive, and variance parameters will be estimated using restricted maximum likelihood method with the Satterthwaite approximation. First, the VLNC condition will be compared to the usual brand condition; if significant differences are observed ($p < 0.05$), the simple effects of visit will be examined within the VLNC condition and the usual brand condition. Biomarkers will be analyzed on natural log scales so that ANOVA model assumptions of normality and equal variances hold. Geometric means in original units will be calculated as well. Interaction terms between BMI and cigarette condition will be added to these models to explore possible moderating effects of obesity on the relationship between cigarette condition and biomarkers. Differences between groups in self-reported quit and cigarette reduction rates at the 4-week post-treatment follow-up period will be evaluated using Chi-square tests, as will be the case for other discrete outcomes such as drop-out rates. SAS (SAS Institute Inc., USA) will be used for most analyses, but may be supplemented by use of STATA or R.

Sample size. Sample size for other analyses was determined using power analysis for hypothesis tests related to the Primary Aim of Study 2, specifically to detect a significant difference between the reduced-nicotine condition and the usual brand condition in the primary endpoints, cigarettes per day (CPD) and urine cotinine, at the end of the trial. Effect size estimates were based on our previous studies of normal nicotine cigarettes (NNC) and VLNC use in disadvantaged women of childbearing age and estimates of CPD in our completed study on smoking topography in pregnant women and women of childbearing age. In that study, pregnant women smoked an average of 12.1 CPD, while preliminary data from our trial of women of childbearing age suggest a decrease of 5 CPD in women smoking VLNC compared to those smoking NNC. A sample size of 45 completers per condition will provide 80% power to detect statistically significant differences in smoking rate.

Potential Risks of Participation

1) Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to significant medical problems including:
    a. Risk to Fetus: 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.
    b. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    c. Respiratory Diseases: Emphysema, bronchitis, and chronic airway obstruction
    d. Cancers: Cancer of the lung, bladder, cervix, esophagus, kidney, larynx, mouth, pancreas, throat, and stomach; leukemia
    e. Metabolic Diseases: Type 2 Diabetes

f. Other Health Risks Associated with Smoking: Including but not limited to infertility, lower bone density in postmenopausal women, and hip fracture in women
g. Death

2) Smoking Withdrawal: Participants may experience smoking withdrawal symptoms during this study. The symptoms can be uncomfortable but are typically of minimal risk. Smoking withdrawal symptoms include:
    a. Anger, irritability, frustration
    b. Anxiousness, nervousness
    c. Depressed mood or sadness
    d. Desire or craving to smoke
    e. Difficulty concentrating
    f. Increased appetite, hunger or weight gain
    g. Insomnia, problems sleeping or awakening at night
    h. Restlessness
    i. Impatience
    j. Constipation
    k. Dizziness
    l. Coughing
    m. Dreaming or nightmares
    n. Nausea
    o. Sore Throat

3) Sample Collection: Breath samples to measure cigarette use and urine tests to confirm pregnancy will be carried out. The results of these tests may be upsetting to participants or cause them discomfort.
4) Survey Questionnaires: The interview will include questions about medical and psychiatric history and questionnaires about mood. Answering these personal questions could make the participants feel uncomfortable. Participants can choose not to answer any questions that make them uncomfortable. If a participant reports thoughts of killing themself of other indicators of suicidality, a study clinician will speak with them. They may also request to talk with a study clinician if they are in discomfort and would like help and/or referrals for mental health resources.
5) Exacerbation of psychiatric symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect psychiatric conditions.
6) Obtaining blood pressure: The blood pressure cuff may cause minimal discomfort. In obtaining blood pressure, researchers may find the participant has abnormal blood pressure. If a participant's blood pressure is abnormal, we will inform them of this and may advise them to see a doctor. Our licensed medical professional may also contact them.
7) 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.
8) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.

9) Undue Influence: Undue influence is a possible risk due to monetary compensation for participating in the study. The likelihood of this risk is low because the compensation is commensurate with the amount of time and effort required for these studies.

Expected benefits of participation:

There are no immediate benefits from participating in the study. The information obtained from this study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health.

Protection Against Risk

Research data without identifiers will be maintained in a locked file cabinet and on password-protected computers in the research staff workplace, with only code numbers identifying subjects. Study consent forms and the linkage between the participants' names and codes will be stored in a locked file cabinet. Interviews with participants will be conducted in private rooms. Urine samples for pregnancy tests and tobacco exposure biomarkers will be obtained in a private bathroom within the laboratory suite. Subjective measures will be administered electronically. The biostatistics and data-management team will provide consistent data-management practices for all data in the Center. Validity and reliability of data will be maximized by using REDCap which, is a secure, web-based system that accommodates local and remote data collection by the project team, and allows for data entry work-flow monitoring and data quality control monitoring by biometry staff. For data integrity, data entry windows will follow the structure of paper forms as much as possible to allow for ease of entry, and will use predefined choices to minimize errors when possible. Data quality monitoring will be facilitated with periodic down loads and analysis using a variety of common statistical program format such as SAS, Stata, R, and SPSS. Quality control procedures will be conducted for all data collected, including analysis of missing data and logic checks for out of range and other anomalous values. This secure electronic data gathering and transmission plan, overseen by the experienced biostatistical team, will minimize opportunities for breaches of confidentiality. Biological samples for nicotine and carcinogen biomarker analysis will be marked with participant ID, stored in the locked laboratory suite, and sent to a laboratory for analysis on a quarterly basis.

All information collected as part of this study will be accessible only to research staff. No information will be shared with participants' clinicians unless the participant requests this in writing. All investigators and staff have undergone (and any new staff will undergo) human subjects' ethics training as required by UVM and are fully conversant with relevant ethical principals around confidentiality. Assessments, consenting and study procedures will be closely supervised by the PI.

The sponsors (NIDA/FDA) as well as the Institutional Review Board and regulatory authorities could be granted direct access to original medical and research records for verification of clinical trial procedures and/or data. If this is required, it will be done under conditions that will protect privacy to the fullest extent possible consistent with laws relating to public disclosure of information and the law-enforcement responsibilities of the agency.

Data Storage:
Data will be stored locally for at least 7 years after study completion at the University of Vermont.

Adverse Events

The research assistant will ask about adverse events at each visit during the study, using a form that assesses the nature, severity, duration, action taken, and outcome of study-related adverse events. AEs will be captured from the time of study consent. Participants will be given contact cards to inform us of events that occur between study contacts. Any AE that remains open will be reviewed and closed at the study completion date (completers, withdrawn, etc.)

All procedures will be monitored to ensure that they conform to the approved protocol. In addition, monitoring will be done of all unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in 38 CFR 46 (death, new or prolonged hospitalization, persistent or significant disability/incapacity); of other significant adverse events (adverse events that lead to drop out by the participant or termination by the investigator); of unexpected adverse events resulting from the study, and of expected adverse events.

Any SAE will be brought to the attention of the site PIs as soon as possible and not longer than 24 hours. Any AE or SAE that is both unexpected and related to study participation will be reported to the IRB within 7 days of the event. The IRB will make a determination as to whether additional reporting requirements are needed. IRB actions will be reported to the funding agency by the PIs no less than annually and more frequently as recommended by the local IRB. Any SAEs will be summarized in the yearly Progress Reports to the funding agency, including a review of frequency and severity. All SAEs will be followed through ongoing consultation with the physician caring for the patient until they resolve, result in death, or stabilize and are not expected to improve. The study staff will be in close contact with participants and health care providers throughout the study to monitor for potential unanticipated problems. Any unanticipated problems will be discussed at the weekly research staff meetings and reported as required to the local IRB.

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) Pregnancy complication: Typically includes miscarriage, stillbirth, or preterm delivery.
2) Cardiovascular disease (CVD) event: Typically includes 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).
3) Deep vein thrombosis (DVT)/pulmonary embolism (PE): I.e., blood clots in the venous system.
4) Suicide attempt: A participant will be withdrawn if she attempts suicide at any time during participation in the study.
5) Psychiatric hospitalization: A participant will be withdrawn if she is hospitalized for psychiatric reasons at any time during participation in the study.

6) Expired breath CO increase: A participant will be withdrawn from the study if the average of two consecutive CO readings during the same visit is more than double their Baseline exhaled CO measurement, or greater than 50 ppm at any given time.

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

1) BP or HR changes: If any of the following occur after informed consent: 1) BP is at or above 140/90 or below 80/50, or 2) HR is at or above 110 bpm or below 45 bpm a manual blood pressure and heart rate measurement will be taken after 10 minutes have passed. If the manual reading is still out of range, a 'Blood Pressure and Heart Rate Symptom Checklist' and 'Medical Event Form' will be completed, and the participant will be monitored by the medical professional.
2) 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.
3) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, etc., then the PI can withdraw her from the study at the PI's discretion.
4) If a participant fails to attend regularly scheduled research assessment visits or comply with the research procedures or schedule, then the PI can withdraw her from the study at the PI's discretion.

Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) has been established to monitor safety outcomes and will be comprised of five members. The DSMB will be chaired by Dr. Kimber Richter, Ph.D., M.P.H., Associate Professor of Preventive Medicine and Public Health at the University of Kansas and Director of the University of Kansas Hospital's tobacco treatment program. Other members include: Kevin Delucchi, PhD., Professor in Residence of Biostatistics in Psychiatry at the University of California San Francisco and Director of the Quantitative Core of the San Francisco Treatment Research Center; Dr. Eden Evins, Associate Professor of Psychiatry at Harvard Medical School and Director of the Center for Addiction Medicine at Massachusetts General Hospital; Hendree E. Jones, Ph.D., Professor of Obstetrics and Gynecology and Director of UNC Horizons at University of North Carolina Chapel Hill; Wallace Pickworth, Ph.D., Research Leader, Baltimore Operation, Centers for Public Health Research and Evaluation, Battelle; Kimber Richter, Ph.D., M.P.H., Associate Professor of Preventive Medicine and Public Health at the University of Kansas and Director of the University of Kansas Hospital's tobacco treatment program.

Conflict of interest

The Board will be convened to serve both studies. None of the members will be otherwise affiliated with the center and each member will complete a conflict of interest disclosure form prior to each meeting. Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired.

Monitoring activities and frequency of meetings

The DSMB will set their own agenda and decisions about monitoring; e.g. how frequently to monitor, what threshold requires changes to protocol or stopping the study, and whether to view raw or analyzed data. The DSMB will be given FDA and EMEA guidelines for DSMBs and recent reviews on DSMBs. A brief

report will be generated from each meeting for the study record and forwarded to each of the study site's Institutional Review Boards (IRB) and NIDA's Program Officer with the progress report. 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 experiences of participants, they will make appropriate recommendations for changes in protocol, as needed. The project investigators will continue to examine safety data, blind to study condition, in case they wish to make study modifications. Before modifications are made, they will inform the DSMB and request their comments.

Communication plan to IRB, NIDA, and FDA (if applicable)
All IRBs, the FDA and the NIDA's Program Officer will be informed of any significant action taken as a result of the Data and Monitoring Board's findings. Study Participants will be informed of any changes in risk.

Protection of confidentiality
For DSMB meetings only de-identified data, including blinded study site and condition type, will be provided to the board. All data and discussion during the meeting will be confidential.

Investigational Tobacco Product

The Vermont Center on Tobacco and Regulatory Science has received an Investigational Tobacco Product (ITP) application from the FDA to cover the experimental cigarettes being used in this study. This application encompasses both Project 4 sites.

Certificate of Confidentiality

To help protect the participant's privacy, Dr. Stephen Higgins, PhD, has received a Certificate of Confidentiality from the National Institutes of Health. 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 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 abuse or a participant's threatened violence to self or others.

Outcome Variables

Primary Endpoints for Study 1:

1) Nicotine withdrawal (i.e., MNWS)
2) Rank ordering of ability of each nicotine cigarette dose to substitute for usual brand dose cigarette

3) Establish cross-price elasticity for each nicotine dose

Primary Endpoints for Study 2:

d. Number of cigarettes smoked per day: study cigarettes, combined study and non-study cigarettes
e. Measure of exposure (i.e., urinary cotinine, expired breath CO, nicotine dependence)

Secondary Endpoints for Studies 1 and 2:

1) Measures of adherence: non-study cigarette use, drop-out rate
2) Measures of psychiatric symptoms: BDI, OASIS
3) Measures of discomfort/dysfunction: MNWS, QSU-brief
4) Measures of other health-related behaviors: weight (Study 1 only)
5) Measures of nicotine/tobacco dependence: FTND, WISDM-brief
6) Measures of tobacco exposure: CO, total nicotine equivalents, NNN, NNAL, minor alkaloids
7) Measures of intention to quit: Stages of Change, Contemplation Ladder
8) Measures of compensatory smoking: puff topography, filter analysis (Study 1 only)
9) Measures of other tobacco use: TLFB-other tobacco
10) Measures of cigarette characteristics: CES, CPT
11) Measures of cognitive function: BRIEF-A, EQ-5D, TPQ, D-KEFS, WASI-II, DDT, SST (Study 1 only)
12) Measures of cardiovascular function: heart rate, blood pressure, urine 11-dehydroTXB2
13) Measures of perceived risk: Perceived Health Risk Questionnaire
14) Safety outcome variables: Adverse Events (AEs), Serious Adverse Events (SAEs)

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