RESEARCH PROTOCOL OUTLINE

**Title of Project:** **Cigarette Smoking in Young Adults (Project ENHANCE)**

**Principal Investigator:** Amy Cohn, PhD, Department of Pediatrics
**NIH Grant Number**: R01DA050990-01

## Abstract

The FDA has announced its intention to reduce the nicotine content in cigarettes[7] as a strategy to promote cessation and reduce smoking-related harm.[8,9] Notably, a low nicotine product standard will apply to all cigarettes on the market, including menthol cigarettes, which account for approximately 30% of the cigarettes used by smokers.[10] Menthol cigarette smoking has increased in young adults (YA; defined here as ages 18-26), while non-menthol smoking has decreased in this age group,[1,2] and the majority of new YA smokers initiate with a menthol cigarette.[3] Additionally, according to recently published data, adults aged 26-34 have shown a rapid increase in menthol cigarette use from 2008 – 2019, compared to adults ages 18-25, and that menthol use was most common among adults aged 18-25 and 26-34 years . Experimentation with menthol cigarettes is linked to smoking progression,[11,12] and greater nicotine dependence relative to non-menthol cigarette use.[1,4,5] If menthol very low nicotine cigarettes (VLNCs) remain more appealing than non-menthol VLNCs, this would indicate that some aspect of menthol maintains smoking behavior even in the absence of nicotine. Results will also further support FDA's regulatory authority to ban or restrict the sale of menthol cigarettes, in addition to market-wide reductions in nicotine content of cigarettes.

This study will recruit a sample of 132 "someday/everyday" menthol smokers aged 18-34 years to capture smokers early in their smoking trajectory. The study will measure reinforcement for smoking experimental (SPECTRUM) menthol and non-menthol very low nicotine cigarettes (VLNCs; 0.4mg) and the impact of proposed product standards and policy scenarios on tobacco product purchasing behavior using a validated Experimental Tobacco Marketplace (ETM).[13-16] Reinforcement across product standards will be assessed using complimentary measures with puff topography measures in a controlled laboratory and using ecological momentary assessment (EMA). We have received supplemental funds to this project from the NIH to add an additional sample of n = 40 sexual and gender minority (SGM) smokers. These individuals will complete the same protocol. Therefore, a total sample size of 172 YA ages 18-26 and adults aged 26-34 years "someday/everyday" menthol smokers will be recruited.

Due to the sensitive nature of items included in the inclusion/exclusion criteria, screening participants who appear to be eligible for the study will have additional screening questions concerning medical history, current mental health status, current suicidal ideation, and past 10-year suicide attempts. Those found to have medical conditions that would preclude successful completion of the study sessions, untreated or worsening mental health concerns, current suicidal ideation,

or past 10-year suicide attempt(s) will not be eligible for the study and will be withdrawn at baseline. An additional 88 participants will be added to the study recruitment analytic sample size goal of 172 YA ages 18-26 and adults aged 26-34 years to accommodate for participants found ineligible at baseline. Therefore, the total enrollment (as defined by The University of Oklahoma Health Sciences Center Institutional Review Board) goal will be a maximum of 260 YA ages 18-26 and adults aged 26-34 years "someday/everyday" menthol smokers.

## A. Specific Aims

**Aim 1:** Determine the influence of menthol flavoring on smoking reinforcement in the context of a reduced nicotine standard in the laboratory. Abstinent smokers (> 12 hours) will attend four laboratory visits. Following a 7-day baseline period of usual brand smoking at home, smoking session 1 will measure reinforcement of one's usual brand cigarette via ad-libitum smoking, where subjective response (satisfaction, craving reduction, psychological reward, sensory effects like throat hit), smoking exposure (CO boost), and behavior (number of puffs, puff volume) will be measured. Following smoking session 1, participants will then undergo two experimental conditions (counterbalanced) in their home environment and the lab for 7 days each: (1) 7 days smoking menthol VLNCs; (2) 7 days smoking non-menthol VLNCs. Participants will be instructed to switch their usual cigarette for the assigned cigarette for each 7-day period (allowing for other product use during that time without specific instruction to model real world behavior). Each condition will be separated by a 7-day wash-out period. On the last day of each condition (smoking Visits 2 and 3), participants will smoke the assigned research cigarette in the laboratory, and data on subjective response, smoking exposure, and behavior will be measured. Hypothesis: Craving reduction and positive subjective response will be greater for menthol VLNCs compared to non-menthol VLNCs, but lower compared to usual brand.

**Aim 2:** Determine the influence of menthol flavoring on smoking reinforcement in the context of a reduced nicotine standard in the natural environment. During each 7-day period of exposure, participants will complete assessments of cigarette and other tobacco use, withdrawal, and subjective response (satisfaction, craving reduction, reward, sensory effects) via twice-daily EMA. Hypothesis: Cigarettes per day, craving reduction, and positive subjective response will be greater for menthol versus non-menthol VLNCs, but lower compared to usual brand. Per previous work, ATP use will be greater in both VLNC conditions compared to usual brand. Effects of menthol vs non-menthol VLNCs on withdrawal, mood, cigarette compliance, and ATP will be compared.

**Aim 3**: Determine the influence of a menthol flavor ban on tobacco purchasing behavior in the context of a reduced nicotine standard using an ETM. At Visit 5, participants will complete two ETMs in the laboratory to model the impact of menthol flavoring and nicotine content on cigarette purchasing in the context of all available tobacco products currently on the market. ETM 1 will evaluate willingness to purchase and smoke non-menthol VLNCs at increasing prices under the scenarios where a

nicotine reduction policy is in effect and menthol is banned in combustible cigarettes. ETM 2 will evaluate willingness to purchase and smoke menthol vs non-menthol VLNCs at increasing prices under the scenario where a nicotine reduction policy is in effect but menthol in combustible cigarettes is available. In both ETMs, all ATPs will be available in different flavors, including menthol, to simulate the real-world marketplace. Hypothesis: In ETM 1, YAs will be more likely to choose an ATP than purchase any cigarettes. In ETM 2, YAs will be more likely to purchase menthol VLNCs or ATPs than purchase non-menthol VLNCs or no tobacco products.

Exploratory Aim: Determine the influence of a menthol flavor ban on tobacco purchase behavior when menthol is banned in all combustible tobacco products (cigarettes, cigars), but is available in non-combustible products (e.g., e-cigarettes).

The proposed research design is unlike existing research, as it combines rigorous, controlled laboratory paradigms of smoking response with "real-world" measurements of the same to determine the relative impact of menthol characteristics and nicotine on cigarette smoking in YAs, a vulnerable group of tobacco users, and adults aged 26-34, who also have high rates of menthol cigarette use. Beyond informing policy, this proposal will validate a new set of measures to be used in future studies to evaluate the potential impact of tobacco policies (e.g., a ban on all flavors) on YA cigarette and alternative tobacco use behavior.

## B. Background and Significance

Menthol cigarette smoking is linked to initiation and progression in young adults (YAs). Although the US Food and Drug Administration (FDA) banned characterizing flavors in cigarettes, menthol cigarettes are still available to consumers. The FDA has recently released an Advanced Notice of Proposed Rule Making (ANPRM) seeking comment on the role of menthol, with the potential for menthol to be limited or banned in some or all tobacco products. Recent studies show that menthol cigarette smoking has increased in young adults (YAs; defined here as ages 18-25) and adults aged 26-34[1], while non-menthol smoking has decreased in this age group.[1,2] Further, national data show that the majority of new YA smokers initiate with a menthol cigarette3 and that menthol cigarettes are the most popular flavored tobacco product used by YAs and adults aged 26-34.[17,18] Menthol flavoring has been hypothesized to mask the harshness of inhaled cigarette smoke,[19,20] making it easier for new users to initiate smoking.[21,22] This likely enhances their appeal and increases curiosity and experimentation with smoking. Experimentation with menthol cigarettes is linked to progression to regular smoking and greater nicotine dependence compared to experimentation with non-menthol cigarettes.[1,4,5]

Very low nicotine cigarettes (VLNCs) may improve public health. The FDA has announced its intention to set product standards to reduce the nicotine content in cigarettes available in the US to a minimally addictive or non-addictive level[7] as a

strategy to promote smoking cessation and consequently reduce smoking-related harm among adult smokers.[8,9] This regulatory action may also deter initiation and uptake of cigarettes by reducing their overall appeal to younger users.[23] Previous clinical trials, including work conducted by our own study team, report reductions in cigarettes per day , biomarkers of toxicant exposure, and increases in smoking quit attempts among adult and adolescent smokers[24-29] using very low nicotine cigarettes. Notably, a low nicotine product standard will apply to all available cigarettes on the market; including menthol cigarettes, which account for approximately 30% of the cigarettes used by smokers in general. However, all clinical trials of reduced or very low nicotine cigarettes (VLNC) thus far have modeled a scenario in which menthol cigarettes are still on the market. Evaluations of VLNCs in younger smokers who prefer menthol, under the policy scenario where menthol is not available, are needed to demonstrate that FDA's proposed product standard will have the intended benefit on public health, and deter initiation and uptake.[11,30,31]

Gaps and limitations in the literature. Although reducing nicotine is likely to reduce smoking in established smokers, it is not known how a menthol ban may interact with a low-nicotine product standard to alter smoking behavior in inexperienced smokers who prefer menthol cigarettes. Thus, a key unanswered question is whether menthol sustains or increases the reinforcing properties of cigarette smoking despite a low-nicotine product standard. If smoking VLNCs compared to normal nicotine cigarettes (NNCs), regardless of flavor type significantly reduces appeal and use of cigarettes, then FDA's implementation of market-wide reductions in cigarette nicotine content could be an effective means to reduce initiation and progression of cigarette use among younger users - specifically those who prefer smoking menthol cigarettes - without the need for a menthol ban. However, if menthol VLNCs remain more reinforcing and appealing than non-menthol VLNCs, this would indicate that some aspect of menthol maintains smoking behavior even in the absence of nicotine, and further supports FDA's regulatory authority to ban or limit menthol in cigarettes, in addition to market-wide reductions in nicotine content of cigarettes.

Understanding the abuse liability of menthol VLNCs in young adults and adults who have high rates of menthol cigarette smoking. The subjective appeal and reinforcing effects of smoking are important indicators of the neurobiological systems that underlie addiction and abuse liability,[32] and have been shown to motivate subsequent smoking. While controlled investigations have examined the differential reinforcing effects of smoking VLNCs vs NNCs, [24-29] the majority have focused on established adults smokers but omitted YA new smokers, and few, if any, have specifically examined differential appeal for smoking menthol vs non-menthol VLNCs.[6] This is particularly noteworthy given the highly appealing nature of menthol cigarettes as a "starter product" for YAs and tobacco company literature suggesting high curiosity and appeal for flavors in this age group.[22] Further, recent evidence shows that menthol cigarette smoking has increased in popularity in adults ages 26-34. Notably, Co-I Cassidy and

colleagues[24] found significantly greater reduction in positive effects of using VLNCs among YA smokers compared to older adult smokers, suggesting that a reduced nicotine standard could reduce smoking reinforcement in this vulnerable population. However, this study did not examine whether menthol VLNCs remain more appealing than non-menthol VLNCs. Establishing a link between menthol cigarette appeal and the nicotine content of those cigarettes in younger users is crucial for determining the abuse liability of menthol VLNCs and the effects of banning menthol in addition to reducing nicotine in cigarettes on population health.

Drawing on the Dual-Reinforcement Model of Smoking as the scientific premise to understand the effects of a menthol ban on a reduced nicotine standard,[33] this study uses a multi-method design to measure appeal/reinforcement and abuse liability of menthol vs non-menthol VLNCs that addresses prior studies' methodological limitations and will inform FDA regulation of tobacco products. We will recruit 172 menthol smoking YAs and adults aged 26-34 who started smoking regularly ("somedays/everyday") < 6-months ago, and assess appeal/reinforcement to smoking SPECTRUM menthol and non-menthol VLNCs (0.4mg/g) and the impact of smoking appeal/reinforcement on tobacco purchasing behavior using a validated Experimental Tobacco Marketplace (ETM) task.[13-16] The ETM will allow us to anticipate how smokers will respond to new product standards and policies after experimenting with these products: one in which nicotine in cigarettes is reduced; and one in which nicotine in cigarettes is reduced and menthol is banned. Appeal/reinforcement will be assessed via complementary measurement paradigms: one in the laboratory using puff topography measures and the other in the natural environment, using ecological momentary assessment (EMA).

An additional 88 participants will be added to the study recruitment analytic sample size goal of 172 YA ages 18-26 and adults aged 26-34 years to accommodate for participants found ineligible at baseline. Therefore, the total enrollment (as defined by The University of Oklahoma Health Sciences Center Institutional Review Board) goal will be a maximum of 260 YA ages 18-26 and adults aged 26-34 years "someday/everyday" menthol smokers.

After smoking their preferred/usual brand in their home environment for 7-days (baseline period) and then in the laboratory ad libitum, participants will undergo two experimental conditions of smoking menthol and non-menthol VLNC SPECTRUM cigarettes (order of administration will be counterbalanced) in their home environment for 7 days each and then in the lab. The two experimental conditions will be separated by a 7-day wash-out period, where they will be asked to smoke their usual brand, as usual. On the last day of each experimental condition, 12-hour abstinent participants will smoke the assigned research cigarette in the laboratory, and data on toxicant exposure (i.e., boost in exhaled carbon monoxide), appeal/reinforcement (i.e., subjective response), and smoking topography measures will be collected. During each 7-day period of exposure and

take home use of SPECTRUM cigarettes, participants will be instructed to switch their usual brand cigarette for the assigned study cigarette and will provide daily data on cigarette use, withdrawal, craving, alternative tobacco use, and subjective response to smoking via two random EMA prompts per day. We will allow for other tobacco product use during the 7-day take home period without specific instruction to align with real-world scenarios, as these products will exist on the market even if a menthol ban and/or a reduced nicotine standard are enacted. We will examine differences in alternative tobacco product use by study condition in exploratory analyses.

At the conclusion of the laboratory and take-home phases, participants will complete two ETMs in the laboratory. The ETM will assess reinforcing value of the study cigarettes smoked by the degree to which they are willing to pay for these study cigarettes at increasing prices, when all other available tobacco products on the market are offered at a fixed price. Participants will be shown a virtual "marketplace" of combustible and non-combustible tobacco products and will be given the option to make purchases of, and take home, the products they would like to use for the week, under two policy scenarios: (1) where menthol and non-menthol VLNCs, but no NNCs or usual brand cigarettes are available in the marketplace, thus modeling a reduced nicotine standard and no menthol ban (on combustible cigarettes); and (2) where non-menthol VLNCs are available, but menthol VLNCs and NNCs or usual brand cigarettes are not available; thus modeling a reduced nicotine standard with a menthol ban on combustible cigarettes. Participants will receive account balances approximately equal to the money they would spend on a week's worth of tobacco. In both ETMs, all alternative tobacco products will be available in menthol and other flavors that are popular. They can purchase as many or few tobacco products as their account balance allow, including no tobacco products; they can 'save' unspent spends. Thus we are able to model the possibility of switching and quitting behavior in response to a nicotine and menthol ban product standard. Participants will be re-contacted 30-days after the ETM visit to assess whether smoking and other tobacco use has returned to baseline levels, and cessation services will be offered.

Due to restrictions on in-person sessions because of COVID-19, virtual sessions will be offered. See section **Protocol Modifications in Response to COVID-19** below for more detail.

This proposal will answer important policy relevant questions about the ways in which menthol smokers could be influenced by FDAs regulatory actions to bring VLNCs to the market AND ban menthol in combustible cigarettes. If smoking menthol VLNCs translates into greater appeal and cigarette consumption relative to smoking non-menthol VLNCs in YAs and adults aged 26-34 who are new to smoking, this provides further evidence that menthol in cigarettes, even with low levels of nicotine, could be a public health hazard. This would support FDA's authority to take additional regulatory actions toward the distribution, manufacture, or marketing of menthol to improve public health. These actions

could include extending the flavored cigarette ban to cigarettes (distribution), restricting menthol cigarette sales to adult-only venues (distribution), limiting the amount of menthol allowed in cigarettes (manufacture), and reducing menthol appeal through public health campaigns or warnings (marketing).

**Conceptual Framework and Scientific Premise.**
The scientific premise for this study relies on Dual-Reinforcement Model of Smoking.[34] According to this model, nicotine has two key effects on reinforced behavior: (1) nicotine acts as a primary (unconditioned reinforcer) that can support the establishment of associated stimuli as conditioned reinforcers, and (2) nicotine enhances the effectiveness and reward value of non-nicotine reinforcers directly, through non-associative mechanisms. The latter is exemplified by studies in which nicotine, administered in a manner unrelated to any cues or behavior, increases operant responding for both unconditioned and conditioned reinforcers.[35-38] As applied to the current study, this model proposes that menthol smoking is a function of menthol acting as a conditioned reinforcer, as a consequence of its association with nicotine (and possibly other primary reinforcers, e.g., sweeteners) and because nicotine may further enhance the conditioned reinforcing effects of menthol.

Tobacco companies have long manipulated the sensory characteristics of cigarettes, including menthol, to encourage smoking.[39-44] Menthol adds a pleasant minty flavor to tobacco and it also imparts a cooling and anesthetic sensation in the mouth and throat, masking the harshness of inhaled cigarette smoke.[12] The conditioned reinforcing effects of the sensory aspects of smoking and nicotine delivery, when paired with the pleasurable taste and sensory effects of menthol (e.g., throat grab) enhances the rewarding effects of smoking (conditioned reinforcer).[32,33] This pairing between nicotine delivery and menthol likely strengthens the learned association between smoking and reward, beyond nicotine alone. As such, even low doses of nicotine paired with menthol could maintain the potency and reinforcing value of smoking because menthol is naturally pleasant, or because menthol has become a conditioned reinforcer that will perpetuate smoking behavior even in the absence of nicotine. If this were the case, it could mean that FDA's attempts to reduce nicotine in cigarettes may have little impact on reducing appeal to smoke if menthol is not also targeted. This has not yet been examined.

Our hypotheses about the subjective appeal /reinforcing value of menthol and the effects of this appeal/reinforcement on response to smoking VLNCs in YAs and adults aged 26-34 are based on the Dual-Reinforcement Model of Smoking and on research in this age group that shows the following. (1) YAs score particularly high on self-report measures of hedonism (i.e., motivated by a strong desire to engage in pleasure-seeking and reward-enhancing behavior) - a central factor of our theoretical model – and hedonism in this age group is correlated with and predicts future health-risk behaviors, including tobacco use.[45-48] (2) Our own analysis of data from the PATH study, which shows that youth and YAs who

initiate smoking with a menthol cigarette are more likely to report a pleasant first smoking experience;[49] and this pleasant first smoking experience is associated with increased odds of reporting past 30-day cigarette smoking and past 30-day use of non-cigarette tobacco products.[49] (3) Literature reviews of tobacco company documents reporting that menthol cigarette marketing campaigns and tobacco companies continue to target consumers, particularly younger ones, with themes of freshness, coolness, crispness and cleanliness,[22,44,50-52] all positive sensory aspects that were used by YA menthol smokers to describe menthol smoking in a recent qualitative study.[49,53] and (4) recent evidence showing a rapid increase in menthol cigarette smoking among adult smokers ages 26-34. Thus, we hypothesize that YAs will show higher levels of appeal and reinforcement for menthol vs non-menthol VLNCs, both in the laboratory and via EMA, and appeal/reinforcement for menthol will be linked to purchase behavior on the ETM. Findings from this previous research and our theoretical model provided the foundation for our methodology and design.

A.3. Complementary Measurements of Cigarette Appeal/Reinforcement

Laboratory Assessment – Absolute Appeal/Reinforcement. Laboratory studies provide a great deal of efficiency and internal control, allowing for causal inference of exposure to toxins in tobacco smoke and acute subjective response to smoking as a function of how a cigarette is smoked (e.g., puff volume, duration of smoking, number of puffs), information that cannot be captured through subjective self-report. Assessing cigarette smoking in the laboratory allows for the detailed and precise measurement of a range of puffing behavior (e.g., puff volume, inter-puff-interval) in responses to different cigarette types; product factors on which tobacco companies capitalize.[22,44,50,54] Previous research shows that smoking behavior in the laboratory predicts changes in plasma nicotine and exhaled CO, and differences in subjective assessments of the tobacco product being measured, including studies of VLNCs.[44,54-57] These laboratory studies have led to an understanding of the craving reduction and satisfaction differences across menthol and non-menthol cigarettes and the thresholds of menthol and nicotine on subjective responses to cigarette smoking.[56,58-64]

Ecological Momentary Assessment (EMA) – Subjective Appeal. EMA allows for similar causal sequencing of behavior measured in the tightly controlled laboratory setting, but in the smoker's natural environment. EMA has several advantages over survey data collection methods[65]: (1) data are recorded in "real time" and in the natural environment, enhancing external validity; (2) data are time-stamped, maintaining sequencing of behavior; and (3) individual as well as group-level behaviors can be examined with greater precision than one-time assessments or longitudinal assessments that are taken weeks, months, or years apart.[66] There are discrepancies between EMA reports of substance use behavior and retrospective reports of the same events, indicating that data revealed through EMA are qualitatively different than what is collected through traditional retrospective reports,[66-68] and would add significant value to our understanding of processes related to appeal and abuse liability of cigarette smoking in YAs and

adults aged 26-34, beyond what we already know.[69] EMA provides a unique method to examine the effect of subjective appeal in the natural vs laboratory environment and the variability in ratings of appeal across cigarette type (menthol vs non-menthol), situations, and days. In this proposal, we will use a well-validated smart-phone based EMA application,[70-74] in which participants read assessment items displayed on their mobile phone screen and touch the screen to select answers. The PI is using this application in her ongoing R01 with YAs.

Behavioral Economic Assessment – Relative Appeal/Reinforcement. Behavioral economic theory assumes that appeal, or reinforcing value for drugs is best measured by examining the degree of resource allocation towards drugs, and the extent to which consumption is sensitive to contingencies, such as price, availability, and/or degree of effort to obtain that drug.[75,76] One recent study by our team's Co-I, Dr. Cassidy, showed that adolescent smokers who used VLNC cigarettes following overnight abstinence demonstrated reduced behavioral economic demand for VLNCs relative to their usual brand.[25] In this proposal, we use a well-validated ETM,[75,77-81] which systematically manipulates the availability and characteristics of tobacco products that align with different policy scenarios. By doing so, the ETM allows for estimation of the relative impact of these characteristics on decision-making (e.g., desire to purchase and use the product with the specific characteristics) as a method of determining how these stimuli impact user appeal and thus reinforcing value. The ETM simulates real-world experiences, in which users are simultaneously exposed to multiple available tobacco products and can "control" their cigarette consumption by changing their use patterns (e.g., switching to non-cigarette products, quitting) if, for example, menthol flavoring and/or NNCs were to be restricted.[82,83] The ETM used in the current proposal allows us to measure the choice of one reinforcer (e.g., menthol VLNCs) as a function of the presence of alternative(s) (e.g., non-menthol VLNCs), thus having direct policy implications.[84-88] Further, in our ETM tasks, participants are given the option not purchase any of the available tobacco products, thus allowing us to model quitting behavior in response to product standards. The underlying assumption of the ETM is that participants are willing to pay more for one commodity (e.g., menthol VLNCs) versus alternative commodities (all other tobacco products on the market) if they perceive that commodity to be more appealing/reinforcing.[88,89]

## C. Preliminary Studies/Progress Report

C.1. Relevant Experience and Preliminary Data. This study builds on our expertise and ongoing work in EMA, menthol cigarette smoking in YAs, and assessment of VLNC appeal in the laboratory and via behavioral economic paradigms with adults and adolescents. The Principal Investigator (PI), Dr. Amy Cohn is an Associate Professor in the Department of Pediatrics at the University of Oklahoma Health Sciences Center and the Oklahoma Tobacco Research Center (OTRC). She is an expert in the assessment of mechanisms underlying appeal for flavored tobacco products using laboratory and EMA paradigms, and has nearly a decade of experience recruiting YAs for longitudinal and observational studies of tobacco and other substance use behavior. She has been PI of three NIH/FDA

grants on flavored tobacco product use in YAs that have informed the current proposal; the most recent of which is a currently funded NIDA/FDA R01 that uses both laboratory and EMA methodologies to examine appeal for menthol and non-menthol NNC smoking in YA new initiates to smoking. The current R01 proposal is a natural extension of the PI's ongoing R01, as it seeks to examine menthol's appeal on smoking under several proposed policy scenarios, which the PI's current R01 does not.

Dr. Rachel Cassidy (Co-Investigator) is Assistant Professor at the Center for Alcohol and Addiction Studies at Brown University. She has wide-ranging experience in smoking topography of nicotine and tobacco products, as well as measuring subjective response to smoking VLNCs in youth (ages 15-19). Her ongoing R01 investigates the impact of nicotine reduction on youth use of cigarettes and alternative tobacco products, and uses laboratory, EMA, and ETM assessments to determine whether and how nicotine reduction may lead youth to change their tobacco use behavior. Dr. Eric Donny (Co-Investigator) is Professor of Physiology and Pharmacology at the Wake Forest School of Medicine. His work focuses on understanding how nicotine functions as a reinforcer of tobacco use behavior. With a wealth of expertise in the proposal's content area and methods, Dr. Donny will help guide the methodology and analyses to ensure comparability with existing clinical trials of VLNCs and assist the team in applying the research findings to inform FDA's proposed policy to reduce nicotine in cigarettes. Dr. Rachel Denlinger-Apte (Co-Investigator) is an Assistant Professor in Wake Forest College of Medicine and specialized in ETM paradigms to assess tobacco product choices under different policy scenarios. Preliminary research performed by our team has informed the central questions addressed in this proposal and decisions about recruitment, methods, measures, and analytic strategies. Our experience is bolstered by the track records of our consultants Drs. Andrea Villanti and Dorothy Hatsukami who are experts in correlates and consequences of menthol cigarette smoking in youth and YAs and measurement of responses to VLNCs using laboratory methods, respectively.

Dr. Cohn has extensive experience conducting NIH-funded EMA studies measuring tobacco and substance use behavior in adults and YAs, with protocols comprising 2 to 4 weeks of daily monitoring periods.[111,112] She has been successful at recruiting participants for these studies, which have included YA smokers. The PI's recently completed R21 of marijuana and tobacco co-use in YAs, used thrice-daily EMA for 28-days and showed an average EMA compliance rate of ~70%.

Co-I Donny and Consultant Hatsukami have managed and conducted numerous human longitudinal laboratory studies evaluating the physiological and subjective effects associated with smoking VLNCs in adults. Co-I Cassidy has conducted several studies of the effects of VLNC use on adolescent smoking behavior.[24,25,117] Her recent work shows that following overnight abstinence (using similar abstinence criteria as those proposed here), adolescent daily smokers (ages 15-19, N=50) who smoked one cigarette of varying nicotine content (15.8, 5.2, 1.3, and 0.4 mg/g of tobacco) in the laboratory rated higher

nicotine content cigarettes as resulting in greater reductions in craving and greater increases in both positive and negative subjective evaluations.[24] This study demonstrates that, acutely, VLNCs reduce craving in adolescents as in adults, and are subjectively less satisfying than higher-nicotine cigarettes. Dr. Cassidy is also PI of an ongoing trial investigating the effects of 3-week use of VLNC vs. NNC cigarettes on smoking behavior, toxicant exposure, risk perceptions, and compensatory smoking in adolescent daily smokers (K01 CA189300). Data collection for this trial is ongoing. Taken together, these studies underscore the team's expertise conducting human laboratory studies of response to VLNCs across the age continuum.[58-63] Many have included the same outcome measures as those proposed in the current study.

Dr. Denlinger-Apte recently completed a NIDA-funded grant (R36DA045183) that incorporates the ETM into a multi-session laboratory study to determine what alternative tobacco or nicotine products adult menthol cigarette smokers would purchase under conditions simulating a menthol cigarette ban.

**Research Design and Methods (What, When, How, Where)**

1. **Identify sources of research material in the form of biospecimens, records and/or data from interaction with participants.**

   Data will be acquired through self-report questionnaires, biochemical measures (expired carbon monoxide), laboratory smoking procedures, and laboratory choice procedures (ETM). Biochemical measures will be collected for research purposes only: exhaled carbon monoxide levels, measured with a smokerlyzer machine, either handheld or iCO (Covita) that can be connected to a smartphone.

2. **Describe study design, including sequence and timing of study procedures. Distinguish research procedures from those that are routine care. Provide a flow diagram or timetable.**

**C.4 Overview and Experimental Design.** This study will take place in the laboratory at the Health Promotion Research Center (HPRC), which is specifically designed for the observation and measurement of tobacco use behavior (virtual sessions will be offered due to COVID-19). After a pre-screen/baseline session, participants will abstain from cigarette smoking and other nicotine for > 12-hours (CO-verified ≤6 ppm or >50% reduction in CO from baseline, per Dr. Cassidy's research with adolescents) prior to each of three laboratory smoking visits (scheduled around the same time of day). Participants will also be asked to refrain from using caffeine for an hour before each in person visit. For these visits, they will smoke their usual brand cigarette, one menthol SPECTRUM VLNC, and one non-menthol SPECTRUM VLNC (order of SPECTRUM cigarette smoking will be counterbalanced), and complete measures of subjective response (e.g., smoking satisfaction, craving reduction, psychological reward, sensory effects like throat hit), smoking exposure (CO boost), and behavior (topography: number of puffs, total time smoked). At the

fifth and final in-person visit, participants will return to the laboratory to complete two Experimental Tobacco Marketplace (ETM) tasks (more detail below). This proposal's abstinence requirement is being used in the PI's ongoing R01 and was chosen because it controls for recent smoking exposure, produces optimal levels of smoking motivation that are sensitive to the experimental manipulations,[64,66,158] and prevents greater attrition and non-compliance relative to more prolonged periods.[157] The laboratory assessment protocol will follow procedures developed and executed in past research studies by the team members. We expect a 20% attrition rate over the four visits, based on the team's experience with laboratory protocols lasting a similar length of time and the PI's work with YAs.[9] We expect a final analytic sample size of n = 138.

The figure below is a diagram of the study visits and procedures.

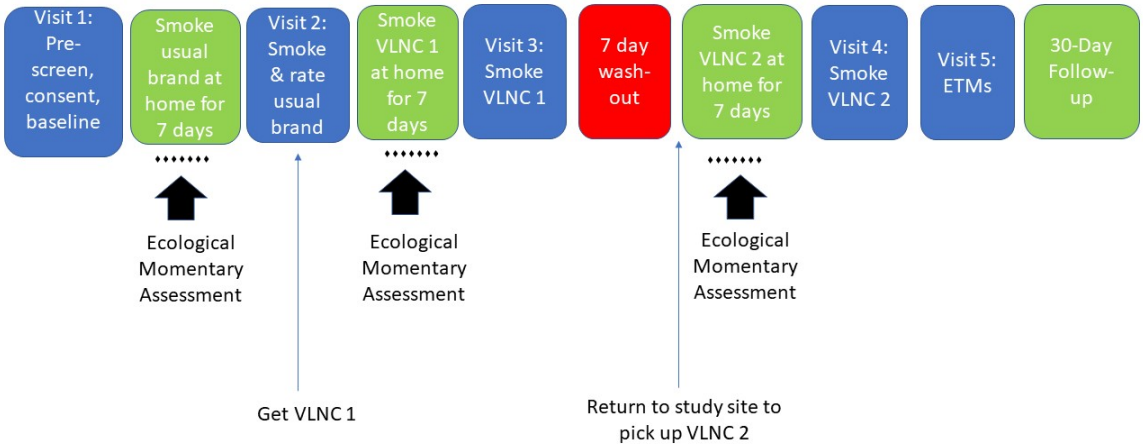


Figure of study design. Boxes in blue indicate in-person laboratory visit; boxes in green indicate ecological momentary assessment/take-home assessment.

## Consent

After a brief screening over the phone, individuals will be provided with a description of the study and procedures. Those who are qualified and interested will be scheduled for a pre-screen/ baseline session. Upon arrival to the baseline session, a member of the research team will review the informed consent with eligible participants to ensure he or she understands the material covered. Participants will be given ample opportunity to read the consent and have any questions related to the consent, the study, or participation answered by the research team member. The participant will have the option to decline participation or withdraw from the study at any time. Individuals will be given as much time as they need to make a decision about participation. If the individual decides to participate, s/he will be given the opportunity to sign the consent and the research team member will sign as a witness. The participant will be given a

copy of the consent form to keep for his or her records. After completing informed consent, a trained member of the research team will verify age and negative pregnancy status (for female participants) before administering the **medical history questionnaire** and **intention to quit smoking log**, the **Patient Health Questionnaire-9** and the **MINI suicidal scale**. A licensed clinician will be available or on-call for the mental screenings should a person report suicidal risk.

Participants will attend five visits to the laboratory and then complete a follow-up assessment 30-days after their last study visit (either in person or remotely) to assess return to baseline smoking and other tobacco use, reactivity (e.g., behavior change) to EMA surveys, complete a third ETM, and will be provided cessation referrals. For each of the in-person smoking sessions (V2-V4), participants will be asked to abstain from nicotine or other tobacco use for a minimum of 12-hours. During all smoking sessions, participants will provide a breath sample to determine expired carbon monoxide (CO) level to measure smoking exposure, and will complete measurements of smoking topography (puff duration, puff volume, inter-puff interval) through a topography machine for each of three sessions. The baseline session will include the informed consent process described above, filling out questionnaires about basic demographic information, health history, smoking patterns and history, and attitudes about tobacco use.

After smoking their preferred/usual brand in their home environment for 7-days (baseline period) and then in the laboratory ad libitum, participants will undergo two experimental conditions of smoking SPECTRUM menthol and non-menthol very low nicotine cigarettes (VLNCs) (order of administration counterbalanced) in their home environment for 7 days and then in the lab ad libitum. The experimental phases of smoking research VLNCs will be separated by a 7-day wash-out period, where participants will be asked to resume the same amount of smoking as the baseline period. On the last day of each experimental condition, 12-hour abstinent participants will smoke the assigned research cigarette in the laboratory, where data on toxicant exposure (i.e., boost in exhaled carbon monoxide) and smoking topography measures will be collected. Participants will also complete questionnaires about smoking urges, withdrawal, mood, and subjective effects of smoking (satisfaction, psychological reward, sensory effects) immediately before and after smoking a cigarette at each visit. Participants will be compensated $35 for the baseline session or $25 if they are deemed ineligible. Participants will be compensated $45 for laboratory smoking sessions 2-4 if they are eligible and $50 for session 5. Participants can receive a $20 bonus incentive if they schedule and attend the first study session with 5 business days of completing the phone screener.

During each 7-day take-home period of smoking SPECTRUM cigarettes, participants will be instructed to switch their usual brand cigarette for the assigned research cigarette and will provide daily data on cigarette use, withdrawal, smoking urge, other tobacco use, and subjective response to smoking via twice daily EMA, as well as other factors related to tobacco use.

**Protocol Modifications in Response to COVID-19**
To prioritize the participants' and the study team's health, the sequence of study requirements may vary due to COVID-19, rules and guidelines set by authorities at the National, Local, or University level. This may mean that the in-person study visits may become virtual (e.g. online video calls) visits. Per our other IRB approved protocols (10581, 10974), the consent and baseline survey will be collected electronically if a participant chooses virtual sessions. Age will be verified before participants engage in their first smoking session if they complete the study remotely/virtually.

**COVID-19 accommodations for measuring smoking behavior and expired carbon monoxide**: Remote topography will be used to allow ambulatory smoking behavior to be recorded remotely from the participant's, if a session is completed remotely/virtually due to COVID-19. The unit will record time, puff duration, volume of smoke inhaled and pressure drops and calculate averages and standard deviations. By using this device, the study will be able to collect smoking topography remotely. Additionally, pregnancy tests will be sent to female participants for exclusion confirmation prior to virtual smoking sessions.

Participants will also be provided a smartphone compatible portable carbon monoxide (CO) monitor (iCO Smokerlyzer) and asked to complete iCOs reading of expired CO to verify smoking status at the beginning of each virtual smoking session (≤6ppm or >50% reduction in CO from baseline) and exhaled CO (exposure) following smoking. Participants will be prompted to connect the iCO device to the study smartphone at the beginning of each study session. They will follow step-by-step instructions to complete the iCO test provided on the smartphone app, and can be assisted by the study staff member during the video call to ensure the device is used correctly. Results of these tests will be date and time stamped. Each participant will be provided their own iCO Smokerlyzer free of charge. This iCO procedure has been approved for use in several other OUHSC IRB-approved studies.

**Research Cigarettes.** We will use combustible SPECTRUM research cigarettes available through the NIDA Drug Supply Program. The VLNC non-menthol and menthol cigarettes will both be 0.4 mg nicotine/g tobacco. These nicotine levels were chosen because prior studies have shown that there is a significant reduction in cigarettes smoked per day and biomarkers of nicotine exposure compared to normal nicotine content cigarettes at this level. Further, it has been proposed that the maximum allowable nicotine content of cigarettes by FDA will be roughly equivalent to this level.[2] The application to obtain research cigarettes from NIDA will be initiated once the OUHSC IRB has approved the study protocol, as a copy of the Institutional Review Board letter is required as part of this application process.

**Pre-Screening/Baseline Session (V1):**
Following a telephone screen, potentially eligible participants will attend a pre-screen/baseline session either in-person or remotely to confirm eligibility. After completing informed consent, participants will verify age, participants will be asked when they smoked their last cigarette, a baseline carbon monoxide measurement will be taken, and female participants will be asked to verify negative pregnancy status. Participants will then complete a medical history questionnaire, and asked about intentions to quit smoking, mental health with the **Patient Health Questionnaire-9**, and suicide risk using the **MINI Suicide screening** before eligibility can be confirmed. Eligibility determination will be made by the RA based on the inclusion/exclusion criteria. If the participant is deemed initially eligible, the Baseline session will immediately begin. Eligibility criteria will be reviewed by the PI (and the medical monitor, if necessary), to confirm final eligibility for the study, prior to Visit 2. If the participant is eligible after Visit 1 screening procedures, the first baseline session will begin immediately. Participants who are ineligible will be paid $25 and will not complete the baseline procedures. The RA will make the initial determination of eligibility; final eligibility will be confirmed by the PI (and medical monitor if necessary), prior to Visit 2. Eligible participants will move on to complete the baseline surveys, which is a battery of questionnaires assessing baseline characteristics. After these assessments, the EMA application will be loaded onto the participant's phone or a study-provided phone (at their choosing) and participants will be given a 10-15 minute training, as per the PIs previous EMA studies, on how to use the EMA platform. For 7-days following V1, participants will smoke their usual brand cigarette in their home environment, as per usual, and measurements of cigarettes per day, craving, symptoms of nicotine withdrawal, subjective response, and alternative tobacco use will be assessed twice daily via EMA.

**Smoking Session 1 (V2): Usual Brand Smoking.** At the end of the 7-day baseline period of usual brand smoking, > 12-hour abstinent smokers (expired CO ≤ 6ppm) or >50% reduction in CO from baseline, per Co-I Dr. Cassidy's research)[24] will return to the laboratory to assess absolute reinforcing value (ARV) of their usual brand cigarette by having participants smoke one of their usual brand cigarettes (ad libitum) through a transducer-based smoking topography data collection device. The instrument records puff volume, duration and velocity and inter-puff interval for each puff and their aggregate averages. These puff topography measures are useful indices of smoke exposure and are sensitive to differences in smoking behavior that may occur between different cigarette flavoring types.[59,61,124] Puff topography measures will be used to examine whether increased puff volume, duration, and lower inter-puff interval differ across cigarettes as a measure of compensation. Prior to smoking participants will be asked when they smoked their last cigarette. Immediately before and after smoking the following measurements will be taken: heart rate and blood pressure will be assessed (heart rate, but not blood pressure, will be collected for remote sessions), and exhaled carbon monoxide (CO boost).

Subjective response to smoking (craving reduction, psychological reward, satisfaction, sensory effects) using the **Modified Cigarette Evaluation Questionnaire (mCEQ**[138-140]) in addition to the **Nicotine Drug Effects Questionnaire (N-DEQ**), **the Duke Sensory Questionnaire (DSQ)**, and **the Minnesota Nicotine Withdrawal Scale (MNWS)** will be measured immediately after smoking. Exhaled CO will be collected via a Smokerlyzer CO detector (Bedfont Scientific LTD), and measured in ppm immediately before and 10 minutes after smoking. CO boost has been used in previous studies[141,142,143] to index smoke exposure, and will be calculated as the difference between pre- and post-smoking levels.

At the end of V2, participants will receive the first set of assigned research cigarettes and will be asked to smoke those cigarettes in their home environment for 7 days; starting on the day after V2 The ordering of flavor of the research VLNCs to be smoked (menthol and non-menthol) will be counterbalanced and assigned prior to Visit 2 (Individuals who complete the session remotely will be scheduled for a pick-up date to get the VLNCs1). During each 7-day period of exposure, participants will be instructed to switch their usual brand cigarette for the assigned research cigarette and will provide daily data on smoking quantity, craving, withdrawal, subjective response, and alternative tobacco product use via twice daily EMA surveys. We will allow for other tobacco product use without specific instruction to align with the real-world scenario, as these products will exist on the market even if a menthol ban and/or a reduced nicotine standard are enacted. Given the high prevalence of dual and poly-tobacco use in this age group, we will examine change in alternative tobacco product use between conditions as a secondary outcome in exploratory analyses, per Co-I Cassidy's and Donny's previous work. Participants will have a 7-day period wash-out period of return to smoking as usual (own brand of cigarette) between the experimental conditions.

**Smoking Sessions 2 and 3 (Visits 3 and 4): Research Cigarettes.** Study Visits 3 and 4 (V3-V4) will be identical to each other. Participants will return to the laboratory for V3 and V4 at the end of each 7-day period of using the assigned research cigarette in their home environment, and smoke that assigned research cigarette in the laboratory . At each visit, participants will be asked to abstain from cigarette smoking or other nicotine for > 12 hours (verified by expired CO ≤ 6ppm or >50% reduction in CO from baseline, per Dr. Cassidy's research. Additionally, prior to smoking participants will be asked when they smoked their last cigarette.).[24] Before smoking the assigned research cigarette, participants will complete a **cigarette purchase task (CPT),** a behavioral economics-based measure of cigarette reinforcement, which assesses hypothetical demand for cigarettes across a range of prices, and a **cross-price elasticity purchase task**, which assesses hypothetical demand for experimental cigarettes at increasing prices of an individual's preferred brand of cigarettes. Participants will also complete a **perceived health risk survey** for the study cigarettes, **a predicted behavior questionnaire**, an **expected utility questionnaire**, the **American**

**Thoracic Society Questionnaire,** and heart rate and blood pressure will be taken before smoking. They will smoke one assigned research cigarette ad libitum at each visit. Puff topography, subjective response, heart rate and blood pressure, and CO boost will be collected. After smoking, participants will complete **the Modified Cigarette Evaluation Questionnaire (mCEQ**[138-140]**)**, **the Nicotine Drug Effects Questionnaire (N-DEQ)**, **the Duke Sensory Questionnaire (DSQ)**, and the **Minnesota Nicotine Withdrawal Scale (MNWS).** At the conclusion of visit 4, participants will be asked to participate in a brief assessment to query about satisfaction with and reactivity to the daily EMA survey (**post-lab and post-EMA reactivity questionnaire).**

**EXPERIMENTAL TOBACCO MARKETPLACE (ETM)**

**C.6. Laboratory Visit 5 (V5) and ETM Procedure**. Participants will complete the ATSQ, mFTQ, MNWS, and QSU after which two separate ETM[3-6] tasks (counterbalanced) will be administered at the conclusion of the laboratory and take home trials (V5) to >12 hour abstinent participants. In the tasks, participants will be shown an online virtual 'marketplace' of cigarettes and all combustible and non-combustible tobacco products that are available on the market. Participants will be instructed to complete the task as if they were purchasing the products from a retailer, and told to make purchases of cigarettes and/or alternative tobacco products that they would take home and use for the week. The price of cigarettes will increase over eight trials ($0.12, $0.25, $0.50, $1.00, $2.00, $4.00, $8.00, and $16.00 per cigarette). The prices of alternative products available on the market will remain fixed, and will reflect the average cost of these products in Oklahoma. The first iteration of the task (ETM 1) will assess participant's willingness to purchase non-menthol VLNCs at increasing prices, where no other types of cigarettes will be available (e.g., menthol NNCs; menthol VLNCs); this will model a scenario where a nicotine reduction policy is in effect and menthol in combustible cigarettes is banned. Findings from ETM 1 will inform FDA whether the presence of menthol-containing tobacco products, beyond cigarettes, leads to significant changes in combustible and non-combustible product use. The second iteration of the task (ETM 2) will assess participant's willingness to purchase menthol VLNCs at increasing prices, where non-menthol VLNCs are available but no other cigarette types (e.g., NNCs) are available; this will model a nicotine reduction policy without a menthol ban. The prices for non-menthol VLNCs in ETM 1 and menthol VLNCs in ETM 2 will be presented at increasing prices. All alternative tobacco products presented in the ETMs will be available in different flavors, including menthol, to simulate the real-world marketplace.

Participants will receive account balances approximately equal to the money they spend on tobacco in one week. They will be instructed that they can 'save' unspent money, and purchase as many or few tobacco products as their account balance allows, including no tobacco products at all. Results of the ETM will not be actualized – meaning the ETM will be hypothetical and they will not receive

the products in their account. Real-world brands of each product type will be presented in the ETM and chosen from those with the highest grossing product sales at the time of funding. The ETM tasks will serve as a controlled assessment of tobacco decision-making processes (e.g., alternative product use behavior) to be compared with patterns of product use generated from laboratory and EMA assessment in the field.
Participants can complete the ETMs in person or remotely, online.
The following images of tobacco/nicotine products will be shown in the ETM:
a) SPECTRUM Study cigarettes menthol OR non-menthol flavors, depending on the ETM;
b) Little cigars
c) Cigarillos
d) E-cigarettes (e.g., cigarette-like systems such as Juul and tank-like systems such as NJOY prefilled tanks)
e) Snus;
f) Conventional smokeless tobacco products
g) Non-prescription medicinal nicotine (e.g., 2mg and 4mg nicotine gum; 7, 14 and 21 mg nicotine patch) menthol and regular flavors
h) Large Cigars
i) Hookah/shisha
j) Tobacco free nicotine pouches

**30-DAY FOLLOW-UP**
A month (30-days) after the final study visit, participants will complete the smoking stages of change, mFTQ, and ATSQ before completing a third ETM in which will assess appeal for non-menthol VLNCs in the scenario where menthol is restricted in all combustible tobacco products. Thus, the only product in which menthol would be available in ETM 3 is e-cigarettes. After that, participants will complete a brief survey indicating whether smoking and other tobacco use has returned to baseline levels (**End of Study Questionnaire**). This 30-day follow-up will be offered face-to-face or remotely. at the participant's preference. They will also be provided cessation referrals.

**C.4.e. Research Cigarette Compliance.** Co-I's Cassidy and Donny, and Consultant Hatsukami all have extensive experience measuring and analyzing the impact of noncompliance with research cigarettes in similar trials,[26,144] and their expertise will help ensure that non-compliance is mitigated and controlled to the best extent possible using the following methods. (1) Compliance with research cigarettes has been demonstrated to increase when incentives are provided for using them. This incentive will be a payment made at each in-person session. To reduce distribution, hoarding, and/or overconsumption, participants will also receive a nominal payment for returning unused cigarettes ($0.25/cigarette up to $20 maximum per participant). Participants will be instructed to return all unused cigarettes and empty cigarette packs to the laboratory each week. At each study visit, participants will also be asked to bring all used study and non-study cigarette butts that they have smoked for the past 7 days. They will be given

plastic bags labeled with their study ID number and calendar dates; a single plastic bag will be used to collect the butts for a single day. The payment schedule for returning research cigarettes (smoked or unsmoked) at each in-person visit (in the form of used butts) is as follows: 75-100%, $7; 50-74% returned, $5; 25-49% returned, $2.50; and 0-24% returned, $0. Participants can receive $1 for each returned empty pack, up to $5 maximum. The team has used this strategy to incentivize product accountability in other studies with success. Honesty of reporting will also be encouraged throughout the study. We will examine concordance between EMA reports of cigarettes per day and number of cigarettes returned to verify compliance. (2) Unfortunately, as participants' usual brand cigarettes will exist in the real world, noncompliance can be an issue in all such studies of this kind.[145] However, noncompliance can be used as an index of dissatisfaction with reduced-nicotine cigarettes.[146] Differences in noncompliance across research cigarette conditions will be examined in exploratory analyses in an effort to inform the application of a reduced nicotine product standard and a menthol cigarette ban to age groups that prefer menthol cigarettes.

**C.4.f. Research Cigarette Distribution and Accountability**. Participants will be given enough cigarettes to accommodate usual smoking patterns until the next visit in 7 days (125% of their baseline cigarettes per day, based on the team's previous work). At V2, participants will report the number of cigarettes smoked per day. Based on this number, staff will calculate the number of SPECTRUM cigarettes needed to provide the participant for each 7-day experimental period (# of own cigs smoked per day x 125% x 7 days). At each in-person visit, research staff will complete a 'Product Accountability Log' with participants to record used and unused cigarettes. Any discrepancies in the product dispensed versus product returned will be discussed and recorded in the log. Participants will be surveyed about desire to quit smoking at each in-person visit. If they endorse that they wish to quit, they will be asked if they still want to receive research cigarettes. If they do not, no study cigarettes will be dispensed and the participant will be retained in the study with no penalty and will continue to complete all subsequent EMAs, the ETM, and the 30-day follow-up. Changes in desire to quit and actual quitting behavior will be examined as an outcome in exploratory analyses, where sample size allows. In her ongoing R01, Co-I Cassidy dispenses research cigarettes in this manner to 15-19-year-old daily smokers with approvals from the FDA and her institutional IRB.

**Measures Descriptions**

Participants will complete validated measures from the PhenX Toolkit and the team members' published studies. The following domains will be assessed in the baseline survey: (1) demographics; (2) Tobacco use patterns (age at first use; nicotine dependence (time-to-first use and mFTQ),[145-146] cigarettes per day; alternative tobacco product use; motivation to quit and quit history; peer tobacco use; tobacco marketing/media exposure[133-136]; and weekly tobacco expenditure; (3) Self-reported appeal of menthol cigarettes; (4) Harm perceptions of

menthol/non-menthol cigarettes; (5) Knowledge and attitudes about nicotine and VLNCs; (6) self-reported skin color; (7) cultural identification and experiences of discrimination; (8) delayed discounting, and (9) factors associated with tobacco use (stress, alcohol, marijuana, drug use). Positive and negative characteristics of cigarette smoking will be measured.[137] Positive characteristics will include: satisfying, fun, exciting, interesting, smell good, taste good, friends would like, stimulating, good with a drink, sophisticated, mature, and mild. Negative characteristics of appeal will include: hard to quit, cause cancer, dangerous, bad breath, stupid, addictive, make me cough, harsh, and make me nauseated.

Because of the high prevalence of menthol cigarette smoking among Black/African-American smokers, multiple dimensions of skin color will also be assessed objectively using a dermaspectrometer,[7] which is a non-invasive tool that measures that amount of melanin in the skin. **Dermaspectrometer** skin assessment will be taken one time, either during a study visit, or at a curb-side pickup or dropoff, if the study is taken remotely.

Respiratory symptoms will be assessed using the **American Thoracic Society Questionnaire (ATSQ)**[8]. Participants report the frequency of experiencing each of 8 respiratory symptoms (e.g., morning cough, wheezing, shortness of breath when walking).

**Safety**: Pregnancy tests will be performed for all female participants prior to engaging in a smoking session. The suicide subscale from the Mini International Neuropsychiatric Interview (MINI)[9] will be used to evaluate suicide risk. A licensed clinical practitioner will be available to conduct the mental health assessment (see section F). CO level will be obtained at every session to evaluate level of exposure to smoke; a large increase in CO can be a reason for withdrawing a participant from the study. **The Patient Health Questionnaire** 9-item version (PHQ-9)[10, 11] is a widely used and validated 9-item questionnaire assessing depressive symptoms in the past 2 weeks. This measure will be used for sample description given the high co-occurrence of smoking and depression and will be used to screen out individuals with moderately severe and severe depression. **Brief Medical History** assesses physical and emotional health to establish eligibility for participation. In subsequent, sessions, the **Health Changes Questionnaire** asks whether the participant experienced any changes in his/her physical or emotional health since their last visit, including whether they have visited the doctor, the hospital, or whether they have had a change in any of their medications. Any endorsement of a negative health change will be tracked as an adverse event. The **Adverse Events Questionnaire** asks about adverse events experienced since the last visit.

**Past 7-day tobacco** use will be measured in two different ways. First, at V2 (as part of the cigarette distribution and accountability log) past 7-day tobacco use will be comprehensively assessed using a **Timeline Follow-Back (TLFB)** technique, a reliable calendar-assisted interview validated for estimating daily use

of tobacco and other substances.[12-14] The TLFB will determine: # cigarettes per day; and frequency and quantity of use of all other tobacco products at baseline to determine the number of cigarettes to be dispensed for the experimental conditions. The **7-day Tobacco Use Questionnaire** will be administered at VLNC2 pick-up (between Visits 3 and 4), where there is a 7-day wash-out period and will ask about past 7-day menthol and non-menthol cigarette smoking, frequency of use of other tobacco products, quit attempts in the past 7-days, and use of other tobacco products to quit.

Before smoking the assigned research cigarette, participants will complete a **cigarette purchase task (CPT)**, a behavioral economics-based measure of cigarette reinforcement, which assesses hypothetical demand for cigarettes across a range of prices, and a **cross-price elasticity purchase task**, which assesses hypothetical demand for experimental cigarettes at increasing prices of an individual's preferred brand of cigarettes. Participants will also complete assessment of nicotine withdrawal and craving prior to smoking using the **Minnesota Nicotine Withdrawal Scale (MNWS)**[15] and the **Questionnaire on Smoking Urges**[16]. Heart rate and blood pressure will be taken before smoking (some measurements may not be taken if sessions are completed remotely). After smoking, participants will complete assessments of subjective response to smoking with the **modified Cigarette Evaluation Questionnaire (mCEQ), the Duke Sensory Questionnaire (DSQ), and the Nicotine Drug Effects Questionnaire (NDEQ)**. Participants will also complete the MNWS again.

The **Predicted Behavior Questionnaire** will be asked at the beginning of Visits 3 and 4, prior to when the VLNC is smoked. It asks participants to indicate their intentions to use cigarettes and other tobacco products when cigarettes have lower nicotine content and come menthol or non-menthol flavor. **The Expected Utility Questionnaire** will also be administered at Visits 3 and 4, before participants smoke. This questionnaire asks the degree to which participants would use the study cigarettes they just smoked for the past week (menthol or non-menthol) would help them quitting, be less dangerous than smoking, give up tobacco use, smoker fewer cigarettes, etc.

Participants will report their perceptions of the health risks associated with both their usual brand and their study cigarette brand using the **Perceived Health Risks Assessment**.[17]

## ECOLOGICAL MOMENTARY ASSESSMENT (EMA)

**C.5 EMA Procedure.** Participants will record cigarette smoking and alternative tobacco use, craving, symptoms of withdrawal, and subjective ratings (e.g., satisfaction, reward, craving reduction, physical sensations like throat hit) associated with smoking the most recent cigarette in response to 2 random prompts to their phone each day. We will use a mobile EMA application, in which participants answer a set of survey questions on their cell phone by selecting

responses on their mobile phone screen. Dr. Cohn is currently using this EMA platform in her ongoing R01 with YAs, and it has been used it in many prior studies of smoking behavior.[71,73,74] The selected monitoring schedule was driven by the study aims, and will allow us to capture a random sample of smoking episodes and to characterize variation in smoking reinforcement, craving, and withdrawal within-days and across days.[147,148] Asking participants to record every smoking episode would be too burdensome and could result in substantial attrition. To ensure we capture smoking episodes for smokers who may be exclusively stimulus-based (e.g., morning only, evening only),[149] we will use an adaptive random prompting schedule that is programmed to coincide with the participant's sleep-wake cycle (e.g., time they wake up, time they go to bed), which will be collected at baseline.

Participants will be able to directly access the EMA survey upon receiving a prompt (vibration or "ping") to their phone by touching the screen. EMA entries are expected to last ~5 minutes (based on response times in prior studies conducted by the PI),[111,113] will be date- and time-stamped, and recorded immediately. To enhance compliance, we will provide detailed training on EMA and monetary incentives (see section 2.5. Recruitment and Retention Plan for more detail on monetary incentives). Pre-paid phones or reimbursement for cellular service will be provided (at the participant's choosing). Pre-paid phones will be labeled "government property". At the 30-day follow-up, participants will complete a brief survey of satisfaction with and reactivity to EMA and another ETM where they will select VLNCs when menthol is banned in all combustible tobacco products, including cigarettes, hookah, little cigars, etc., but not banned in e-cigarettes.

**C.5.b**. **EMA Measures.** EMA measurements will parallel the constructs used in the laboratory assessments (e.g., craving, subjective response) and have established psychometric properties.[66,68,111,150-154] Subjective ratings will be queried using items from the mCEQ, which has been pilot tested for EMA deployment by the PI and is being deployed via EMA for her ongoing R01. Questions will also assess the use of alternative tobacco products since the previous assessment, characterizing flavors (e.g., fruit, chocolate), use of usual brand cigarettes, craving, withdrawal, and factors associated with smoking (life events, mood, peer use, alcohol, other drug use) that have been used in prior EMA studies by the PI and others. To minimize response burden, EMA will prompt use-relevant probes via skip patterns. Missed EMA assessments will be retrospectively assessed by phone or online via a REDCap survey.

**Following are the standard procedures that have been adopted for OUM/OUHSC for all studies that will be facilitated in-person and would be utilized for this study in response to COVID-19.**

PROCEDURE:

1. Employees will comply with all OUHSC COVID related policies and procedures as currently exist and as are revised in the future.
2. Efforts will be made to minimize face-to-face time with participants. When possible, consents will be sent to participants at their homes and reviewed by phone or zoom, as available. Additional items, including pregnancy tests, will also be shipped to the home, and reviewed over phone or zoom, when possible.
3. During scheduling, participants will be asked to wear a mask, if they have one available, to their appointments. For participants who do not have access to a face mask, one will be provided. They will also be asked the questions from the OUM/OUHSC COVID19 Questionnaire (see attached in "Other Documents").
4. If the patient is symptomatic or has known direct contact with a person with COVID-19 they will not be able to attend a study session and will be asked to consult with their PCP prior to re-scheduling the visit.
5. Participants will be instructed to call from their vehicle upon arrival for their appointment to prevent participants from congregating in the waiting room. They will also be verbally asked if any of their answers from the COVID-19 questionnaire have changed since their original completion. If the patient is symptomatic or has known direct contact with a person with COVID-19 they will be asked to reschedule their appointment.
6. If a room is not available, the participant will wait in their car and the study coordinator will call them once space is available. We will make every effort to ensure that the assigned research room will be available by spacing apart study sessions.
7. Participants will have their temperature taken using a contactless thermometer prior to entering the facility. If the temperature is above at or above 100.0°F they will not be seen and will be advised to contact their PCP for further assistance.
8. Participants will not be allowed to have a second individual accompany them or wait in the waiting room unless previously approved for special circumstances by study staff.
9. Upon entering research rooms, proper hand hygiene will be executed by study staff and participants. Study staff will be gloved for any touch-related interactions with the participant. Hand sanitizer will be available for participant use as well.
10. Staff will wear proper PPE at all times.
11. To reduce viral transmission, study staff will be seated in a separate room from the research participant during the visit. Communication with the participant will occur by video and audio connection between the staff "control room" and the participant's research room. These sessions will not be recorded. All participants will be placed in a negative pressure room that is specifically designed to circulate the air outside of the room every 10 minutes; thus reducing exposure to viral droplets.
12. To reduce viral transmission during and between shifts and following interaction with participants, all spaces will have available cleaning products containing 70% ethanol to disinfect surfaces, door knobs, and equipment surfaces frequently, between each research participant, and at the beginning and end of a shift and

before and after each participant. Common equipment in shared areas will be disinfected with 70% ethanol prior to and after each use.

**3. Duration and number of study visits required.**

Participants will be involved in the study for approximately 2 months. There will be 5 in-person study visits (or virtual sessions) and a total of 21 days of daily monitoring of cigarette smoking behavior. There will be a 30-day follow-up after visit 5, that will be conducted either in person or over the telephone.

**4. Describe blinding, including justification for blinding or not blinding the trial.**

We considered blinding participants to the nicotine content in the research cigarettes to minimize the possibility that perceptions of these cigarettes may impact ratings of appeal/reinforcement and use behavior (e.g., compensatory behavior). We ultimately chose not blind participants so that we could model real-world conditions in which participants would be aware of the nicotine content of the cigarettes they smoke. Dr. Hatsukami, our consultant, is taking this same approach (e.g., not blinding participants) in a pilot study conducted as part of her U54. While we know about responses to VLNCs in a blinded scenario, findings from our study will be one of the first to inform VLNC work in an un-blinded scenario with young people.

**5. Include justification for inclusion of a placebo or non-treatment group.**

N/A. This is not a treatment study.

**6. Describe what happens to participants receiving therapy when study ends or if their participation in the study ends prematurely.**

N/A. This is not a treatment study.

**7. Indicate where the procedures will be completed.**

All participant recruitment, enrollment and testing will occur at the research laboratory of the TSET Health Promotion Research Center (HPRC) in Oklahoma City, OK. HPRC has conducted smoking research for the past 5 years.

**8. Indicate whether clinically relevant research results, including individual research results, will be disclosed to participants. If so, under what conditions?**

Females will be asked to take a pregnancy test at each in-person (or virtual) session prior to smoking, to determine eligibility. If a woman is pregnant, she will be given the results of her test immediately. If the session is completed remotely,

pregnancy tests will be provided to the participant before the session (mailed or curb-side pick-up) and pregnancy will be confirmed prior to beginning a smoking session.

9. Identifiers might be removed and the de-identified information may be used for future research without additional informed consent from the subject.

## D. Biospecimens

Biospecimens will be collected prospectively. Biospecimens to be collected will be expired breath analysis of carbon monoxide level to determine smoking recency. This is a non-invasive procedure conducted by blowing air through a Smokerlyzer tube. We are also collecting pregnancy tests prior to each smoking visit, to determine study eligibility. Pregnancy tests will be discarded and not kept. All biospecimen data collection will be de-identified and associated only with a unique ID number. The participant's biospecimens (even if identifiers are removed) will not be used for commercial profit. The research will not include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

## E. Banking/Repository/Database

All data collected during the study will be retained for future use in tobacco and nicotine research. Data will be stored electronically on a secure password server that can only be accessed by approved study personnel. Only data, no samples, will be stored.

## F. Inclusion / Exclusion Criteria

1. Inclusion criteria for participants will include:
   a. Ages 18 to 34;
   b. Smoke cigarettes "somedays" or "everyday" for at least the past 3-months;
   c. A strong preference for menthol cigarettes (i.e., smoke menthol ≥80% of the time)[124];
   d. Ability to read English at an 8th grade level or higher; and
   e. No immediate plans to quit smoking.

2. Exclusion criteria for participants will include:
   a. Current use of nicotine replacement therapy (NRT);
   b. Pregnant, planning to become pregnant, or currently breastfeeding (verified by pregnancy test at each study visit/virtual smoking session);
   c. Past or current self-reported clinically significant heart disease or hypertension, or other smoking-related disease (by history) that preclude successful study completion;
   d. Serious psychiatric disorder, as evidenced by any of the following
      i. Ever schizophrenia, schizoaffective disorder, or bipolar disorder;
      ii. Psychiatric hospitalization in the past year;

iii. Suicidal ideation in the past month or any past year suicide attempt
    1. Suicidal ideation determined by the MINI suicide subscale (Questions 1-3)
    2. Any suicide attempts in the past 10 years (MINI suicide subscales Questions 5 and 6)
iv. Suicidal intent and plan (MINI suicide subscale Question 4)
v. PHQ-9 score of 15 or higher, indicating moderately severe depression, if participant also indicates suicidal intent or worsening depression in the past 3-months. Scores of 20 or higher, indicating severe depression will be excluded.
vi. Worsening symptoms of depression or anxiety in the past 3-months (as determined by Medical History Questionnaire).

    If a participant indicates that he/she currently has suicidal ideation during the baseline or any future session, the Suicide Risk SOP protocol will be followed in which a Licensed Clinician will be contacted immediately (if that clinician is not already conducting the assessment). Participants will speak with the clinician in person, over the phone (or via Zoom) and the clinician will determine the appropriate action to take to keep the participant safe. See Suicide Risk SOP for more detail. This SOP follows the same protocol outlined in the OUHSC Tobacco Treatment Research Program (TTRP) and has been approved by the OUHSC IRB.

e. Inability to abstain from nicotine/tobacco products and caffeine prior to study visits;
f. Strong preference for non-menthol cigarettes (smoke non-menthol > 80% of the time)[124]

All participants will need to provide an ID that indicates their age in order to participate. If a participant is enrolled remotely, participants will be asked to email a picture of their ID to the study email, or show an image of their ID to study personnel via a Zoom session so it can be verified prior to being enrolled in the study. Eligible participants will not have immediate plans to quit smoking, and will be "someday" or "everyday" smokers for at least the last 3 months, thus the laboratory and take home smoking will confer no additional risks beyond their usual smoking. We will exclude individuals who report immediate plans to quit smoking or who are currently trying to quit smoking at the screener and baseline, as we do not wish to impede any active quit attempt. We will assess desire to quit smoking at screening and each laboratory visit, and any indication of a desire to quit will result in ineligibility from the laboratory phase of the study if a participant chooses not to continue using the study cigarettes. Participants who choose not to use the study cigarettes will be allowed to remain in the study and complete the remaining study assessments if they desire. Individuals will be provided tobacco cessation resources upon request or at the end of the study (if not provided earlier). We will exclude participants who indicate suicidal ideation

as the potential to undergo nicotine withdrawal may exacerbate symptoms of depression. All female participants will be tested for pregnancy at each smoking visit or session. If a participant becomes pregnant during the study, she will be withdrawn from the study. Individuals will be provided referrals for treatment, where needed or desired, and at the 30-day follow-up. Males and females of any ethnic or racial group are eligible to participate in the study if they meet inclusion/exclusion criteria.

The suicide subscale from the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 2010) will be used to evaluate suicide risk. A licensed clinical practitioner will be on call should a participant endorse suicidal ideation, intent, or plan. If a participant indicates that he/she currently has suicidal ideation during the first or any future session, the Suicide Risk SOP will be followed in which a Licensed Clinician will be contacted immediately, and the participant will speak with the clinician over the phone, in person, or via Zoom. The licensed clinician will determine the appropriate action to take to keep the participant safe.

## G. Gender/Minority/Pediatric Inclusion for Research

The research will not focus on any particular racial or ethnic group. All participants will be between the ages of 18 and34 due to the aims of the study. We expect the racial/ethnic composition of our sample will reflect the composition of the populations from which they are drawn. If eligible, participants will be enrolled without regard to gender or racial/ethnic background. Oklahoma City is diverse, with a population that is 15% African American and 17% Hispanic or Latino, according to 2018 census data. We will try to recruit a sample that is 50% female so that we can examine sex as a moderator of study outcomes.

## H. Recruitment and Enrollment

1. **Describe the plans for recruitment**.

Recruitment will take place through the Oklahoma Tobacco Research Center (OTRC), now called the TSET Health Promotion Research Center (HPRC), in Oklahoma City, OK, using methods that have been used in previous laboratory studies at HPRC: local newspapers (including at local colleges/universities), online (e.g., Craigslist, Facebook, Instagram, Snapchat), community flyers, snowball techniques, , through mass email at the University of Oklahoma (mass email reaches all undergraduate students, > 20k), and a database of interested callers from prior studies. These strategies have been successful at recruiting smokers across the age spectrum for a variety of studies conducted by the team members. Oklahoma City greatly facilitates the successful recruitment of YAs given its close proximity (<10-20 miles) to several colleges and universities, such as the University of Oklahoma, University of Central Oklahoma, Rose State College, Oklahoma City Community College, Francis Tuttle Technology Center, and Oklahoma State University.

Social media recruitment occurs through work with Trialfacts and BuildClinical. Trialfacts and BuildClinical will assist with recruitment by designing and

managing targeted, GCP-compliant, IRB approved advertising. Potential participants who express an interest will click on a Trialfacts- or BuildClinical-generated ad and will be taken to a custom landing page created by Trialfacts or BuildClinical. These landing pages will offer a brief description of the study that is designed to convert interest into engagement. After clicking on a Trialfacts ad, participants will review the Trialfacts Consent to continue (attached as part of the Trialfacts pre-screener) and will only be able to provide their contact information and continue with the Trialfacts pre-screener if they select "Yes" in response to "Are you willing to continue." Individuals who select "No" will not continue with the prescreener. Participants who click on a BuildClinical ad will be presented with a pre-screening form that they will complete which includes contact information so a research technician can contact the potential participant for additional screening.

**Update about the impact of Tobacco 21 regulation on study recruitment**

Because of the new Tobacco 21 regulations at the state and federal level, individuals under the age of 21 are currently not allowed to purchase tobacco products. The Governor of Oklahoma signed a bill into law (SB319) in April 2021. This new law went into effect November 1, 2021 and allows IRB-approved studies to "furnish" tobacco products to individuals ages 18 to 20. As a result, individuals ages 18 to 20 can be enrolled in the study and we are legally allowed to dispense cigarettes to individuals aged 18-20.

2. **Describe the consent procedures to be followed**

Participants will provide verbal or electronic consent if they are screened over the phone or online, respectively. Verbal consent will be obtained for participants completing the telephone screener. Prior to beginning the telephone screener, participants will be told (a) their research data provided on the telephone screen will be confidential and coded only with a unique identifier; (b) their personally identifiable information will be encrypted and can be accessed only by approved study personnel; and (c) there is a possible risk of loss of confidentiality although the risk is considered low given that research data will be de-identified.

Eligible participants who complete the study in person will provide written consent in person immediately before their first laboratory visit begins. This will take place in our lab. We will go over every section of the consent document with the participant, then ask if he or she has any other questions before signing. Each participant will be allowed time to read the consent document and ask questions before any data are collected. A copy of the consent form will be given to the participant.

Per our other IRB approved protocols (10581, 10974), the consent can be collected electronically in the event that sessions are completed virtually due to COVID-19. To provide consent electronically, participants will be sent a link to the eIC via REDCap. REDCap has a feature which allows for version control, automatic time and date stamp, and electronic signature (using a fingertip,

computer mouse, or stylus on a tablet screen). To ensure that the eIC is presented appropriately and that subjects will have enough time to dedicate to the eIC process, an eligible and interested participant will be told by a study personnel, at the end of the phone screening session, approximately how long the consent review process will take and will review with them the information that will be in the eIC. The eIC will record the timestamp of participant's acceptance or declination and a copy of the signed eIC will be sent to the participant via email. No personal information, other than the participant's name, will be collected in the eIC.

Participants will be reminded that their participation is voluntary. Additionally, they will be reminded that they are allowed to discontinue participation in the study at any time, without any loss of benefits or other negative consequences. Participants will be given ample opportunity to read the consent and have any questions related to the consent, the study, or participation answered by the research team member. The participant will have the option to decline participation or withdraw from the study at any time. Individuals will be given as much time as they need to make a decision about participation. If the individual decides to participate, s/he will be given the opportunity to sign the consent and the research team member will sign as a witness. The participant will be given a copy of the consent form to keep for his or her records. All research team members will complete an approved course on the protection of human subjects and be trained on how to clearly describe study procedures and the obtain informed consent process.

**Compensation**

We will use several strategies to encourage completion of the study by providing participants: 1) a calendar of their appointments throughout the study; 2) reminder calls, emails, and/or texts the day prior to a scheduled session; 3) monetary incentives at each visit; and 4) a completion bonus.

All participants will be reimbursed for their participation via cash or reloadable gift card, at their preference. Participants will receive $35 for completing the baseline session. Participants will receive $45 for completing each in-person laboratory smoking visit (Visits 2-4) and $50 for the completing the final in-person ETM session (Visit 5). Participants who attend the baseline session but are determined ineligible during that session will receive $25. Eligible participants who schedule and attend their first visit within 5 business days of completing the telephone screener will receive a $20 bonus.

Participants will be compensated for completing the daily surveys as follows: they will receive $1 for each completed EMA survey (totaling $42), a $10 bonus each week of EMA for completing all EMA surveys in that one week period (totaling $30), and a $45 bonus if they complete 85% of EMA surveys over the courses of three weeks. There will be a brief 30-day follow-up to assess whether smoking

and other tobacco use has returned to baseline levels. This 30-day follow-up survey will also include a post-EMA survey to assess reactivity, or behavior change to daily monitoring; for which they will be paid $45. Participants who refer an individual who is eligible and who signs informed consent to participate will receive a $20 referral bonus (limited to one per participant) and those who complete all phases of the study will be eligible for a $70 bonus.

Per previous studies conducted by the study team's Co-Investigators with adults and adolescents using very low nicotine cigarettes, participants will receive a nominal incentive for returning unused cigarettes, to ensure that participants to not hoard, stockpile, or share cigarettes with others. The compensation schedule for returning unused cigarettes is $0.25 per cigarette, up to $20 per participant; and $1 for returning empty packs, for up to $5 per participant. For returning used and unused cigarettes at Visits 2 and 3, participants will be compensated as follows: 75-100% returned, $7; 50-74% returned, $5; 25-49% returned, $2.50; and 0-24% returned, $0.

Participants will receive $10 for travel for each in person visit (@ 4 visits) or $10 for each curbside pick-up/drop-off of study materials, for a total of up to $40. Curbside pick-up/drop-off can be at the HPRC laboratory location or at another public (e.g. coffee shop, restaurant, convenience store, or shopping center) agreed upon location. Total possible compensation will be $571. Participants are compensated for returning used cigarettes so that we can accurately track and account for used study cigarettes and unused study cigarettes. Participants will be asked to provide their social security number, their residency status (permanent residents must provide a copy of their green card if applicable), and whether they are a University of Oklahoma employee for tax reporting purposes. Participants who are not U.S. Citizens or permanent residents or individuals who are unwilling/unable to provide their residency status, social security number, and whether they are a University of Oklahoma employee will be excluded due to the inability to receive study compensation according to the University of Oklahoma Administrative Policy Part 500 Section 557.

**Table of Compensation Schedule.**

| EVENT | AMOUNT |
|---|---|
| **Laboratory Visit** | |
| Visit 1 (Pre-Screen/Baseline session) | $35 |
| Visit 2 | $45 |
| Visit 3 | $45 |
| Visit 4 | $45 |
| Visit 5 (Experimental Tobacco Marketplace) | $ 50 |
| Bonus for eligible referral | $20 |
| Bonus for scheduling and attending first visit within 5 days of phone screening | $20 |
| **EMA** | |

| | |
|---|---|
| Call completion (*42 calls) | $1/call ($42 total) |
| Bonus for completing all calls each week (* 3 weeks) | $10/week ($30 total) |
| Bonus for completing 85% of calls for 3 weeks | $45 |
| Total possible EMA | $117 |
| **Research Cigarette Compliance** | |
| Returned used cigarettes | $7 maximum/week @ 2 weeks |
| Returned unused cigarettes ($0.25/cigarette) | $20 maximum/participant |
| Returned empty packs ($1/pack) | $5 maximum/participant |
| Total possible cigarette compliance | $14 + $20 + $5 = $39 |
| **30-Day Follow-up** | |
| 30-day Follow-Up + ETM 3 | $45 |
| **Travel for In Person or Curbside Pick-up/Drop-Off** | |
| $10 for each in person visit/curbside pick-up/drop-off of study materials @ 4 visits | $40 maximum/participant |
| Bonus for completing all phases | $ 70 |
| Maximum Total | $ 571 |

To enhance retention in all phases of the study, due to higher than anticipated loss-to-follow-up, we will offer a bonus of missed incentive amounts to participants who are hard-to-reach or schedule. With this bonus, participants will be eligible to receive missed compensation opportunities, if they complete remaining in-person study sessions and/or surveys. Missed opportunities may include the bonus for scheduling and attending the first visit within 5 days of phone screening ($20), the eligible referral bonus ($20), bonuses for completing all EMA surveys each week ($30 maximum) even if they miss some surveys, bonus for completing 85% of EMA surveys for 3 weeks ($45) even if they miss some surveys, and the bonus for completing all phases of the study ($70). Enhancement bonuses will be separated into $20 increments to encourage a participant to attend any remaining session(s) they have not completed. After the final in person session is complete, the participant will be eligible for all remaining compensation amount not already claimed, up to the maximum of $571, even if they may not have met the full criteria. Thus, we calculate their maximum bonus amount allotted to participant, and give it to them in $20 increments (per number of sessions attended). When they complete the final in-person visit, they are eligible for all remaining bonus/compensation to get the maximum amount ($571).

Participants have the option to receive payment via Amazon Gift Card code or reimbursable gift card (Greenphire ClinCard). The university has a Business Associate Agreement with Greenphire. All participants who complete the baseline/pre-screen session remotely will only be paid with Amazon gift card code, to reduce costs associated with mailing a ClinCard to individuals who may not be eligible after the pre-screen session. To set up ClinCard payments, Greenphire is provided the name, birthdate, and address of the participant. Greenphire does not have access to any research data. Participants who report a lost or stolen ClinCard will be given one replacement at no cost to them. The

replacement card will be linked to the existing account and the previous card will be deactivated. Participants who lose a second ClinCard will be given instructions to contact Greenphire to request a replacement card for a $7 fee at their own expense. They may also choose Amazon gift card code for future reimbursement, at no cost to them.

**3. Describe the location where consent is most likely to take place**

Consent will take place at the TSET Health Promotion Research Center.

**4. Describe provisions for recruiting non-English speaking participants.**

Non-English speaking participants will not be recruited into this study.

5. **Describe measures to decrease participant coercion.**

Several recommended approaches will be used to reduce coercion, including allowing participants ample time to review the consent, and using only qualified trained research staff to engage in the consent form process. Further, participants will be told at the screening and at the time of consent that their participant is completely voluntary. They will be reminded at each in-person visit, and at the 30-day follow-up that they can decline to answer any question and they can withdraw their participation at any time without penalty. Individuals will be also told at consent and reminded again at each in-person visit that they can decline to continue using the study product at any time, and still remain enrolled in the study and undergo the study assessments. This will reduce the potential for incentivizing continued smoking.

## I. Risks and Benefits

1. **Describe risks and assess their likelihood and severity**.

The risks in this study are considered minimal and include (1) subjective discomfort from answering questionnaire items or from providing breath samples; (2) risk of breach of confidentiality; (3) issues of coercion; (4) discomfort from withdrawal (e.g., mild irritability, trouble concentrating) due to abstinence requirement or use of VLNCs; (5) the possibility that use of VLNC cigarettes may lead to compensatory smoking or use of alternative tobacco products; (6) the possibility of perceiving a reduced risk associated with VLNCs and smoking a single cigarette in the laboratory. The cigarettes smoked during the course of this study will be either the participant's own brand provided by the participant, or SPECTRUM cigarettes, which are issued by the NIDA Drug Supply Program. Although smoking is associated with disease, we do not expect the disease risk to be significantly greater from smoking the experimental cigarettes.

Subjective discomfort. The likelihood of experiencing subjective discomfort from answering questions is very low and the severity is low, based on our past and

current experience using similar protocols and measures with young adults in our research studies. Discomfort from providing breath samples also is low based on past experience using these measures as well, as our assessment tool is non-invasive.

Breach of confidentiality. The risk of breach of confidentiality is also low, and the severity of this risk is low. The procedures used to protect confidentiality, and the adequacy of the data safety and monitoring plan is outlined below.

Coercion. Coercion is a possible risk due to monetary compensation for participation; however, the likelihood and severity of this risk is low because the compensation is commensurate with time and effort required for this study. Further, participants are reminded at the baseline session, during the consent process and again at each in-person session that their participation is voluntary and that they can decline to use study cigarettes at any time, and remain in the study to complete all subsequent assessments.

Discomfort from withdrawal. The risk of experiencing discomfort from withdrawal is moderate and the severity is considered low. Participants will be instructed to abstain from cigarette smoking and other nicotine/tobacco use for a minimum of 12 hours prior to each in-person study visit. Some participants may experience nicotine withdrawal symptoms including irritability, difficulty concentrating, restlessness, anxiety, and depressed mood. Nicotine withdrawal symptoms can be uncomfortable, but they are not dangerous. Participants will be given information about the possibility of nicotine withdrawal symptoms at the end of the screening (before they attend the first baseline session) and again during the consent process. The likelihood of experiencing withdrawal symptoms from using VLNCs is moderate. In the study, participants will be asked to smoke VLNC cigarettes for 7-days at a time, and are able to return to smoking as usual after that 7-day period, and may experience nicotine withdrawal symptoms such as irritability, negative affect, and craving. Participants are not prohibited from using other nicotine-containing products, which could reduce these symptoms.

Compensatory smoking and/or tobacco use. It is possible that compensatory smoking or increased use of alternative tobacco products may occur. The possibility that use of VLNCs may lead to compensatory smoking is low in this study, especially because these cigarettes are not being used over an extended period of time. While compensatory smoking with VLNC cigarettes has not been observed in adult smokers, it is possible that it may occur in this population. However, in Co-Investigator's Cassidy's current field trial using VLNC cigarettes in adolescents, she has not yet seen significant compensation (N=45 complete); therefore, this outcome is unlikely. The potential for an increase in alternative tobacco product use is moderate. Young adults will report their cigarette use and their use of other tobacco products daily, and their CO levels will be collected at each weekly in-person visit; therefore, we will be able to closely monitor the extent to which compensatory smoking or tobacco use may be occurring and

make changes to the protocol to reduce this as necessary.

Perceived reduced risk of low nicotine cigarettes. The possibility of perceiving a reduced risk of harm with VLNC cigarettes is moderate; the severity of the risk is considered low. We will debrief each participant, post-study on the relative and absolute risks of all products involved in the study. Finally, use of cigarettes will be limited to current smokers with no immediate intentions to quit smoking and will present no increased risk of harm than their current smoking status incurs.

Smoking a single cigarette in the laboratory. Although no exposure to smoking is safe, participants will not be exposed to any more risk than the usual risk they expose themselves to by choosing to smoke. The laboratory where smoking sessions will be completed was constructed with a special ventilation system for quickly removing smoke from the experimental rooms to reduce excess smoke exposure to participants and researchers.

2. **Describe procedures for protecting against or minimizing potential risks.**

Subjective discomfort. Any distress or subjective discomfort from answering questions will be minimized by assurances that participants can refuse to answer any particular question that they do not feel comfortable addressing and may withdraw at any time without penalty. To minimize the risk of discomfort from providing breath sample, only trained staff will conduct all procedures and, as above, emphasize that study participation is voluntary. Participants will be debriefed following each session to determine their level of discomfort and will have the opportunity to discuss any discomfort with project staff.

Breach of confidentiality. Protection of privacy is of the upmost importance. We will implement several practices to ensure privacy protection.

- All paper/pencil participant data will be kept in locked files which are only accessible to project staff.
- Publication of results will be in the aggregate with no identification of individual respondents. No names will ever appear in data sets.
- Participants will provide responses to a series of questionnaires at each study visit. Study records will be collected via a 21 CFR Part 11 compliant electronic data capture (EDC) system called REDCap with a unique study ID for each participant. REDCap has been approved for use in clinical trial data collection by the OUHSC IT.
- Confidentiality will be maintained by numerically coding all data with a unique ID number, using a HIPAA compliant electronic data capture database (REDCap), and keeping data locked in file drawers or on a secure password protected server that can only be accessed by approved study personnel. Names and contact information of participants, including when collected during the screen, will be kept separate from research data in a separate locked drawer or data file on a secure password protected server and

can only be accessed by approved study personnel. Only study research assistants and the PI will have the information that connects participants' names and ID numbers. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical reporting in any publication.

- The following features are designed to ensure the security of the data of the mobile app that will be used for EMA data collection in Phase 2: 1) the data stored on the smartphone device are in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users); 2) a unique password (only known to researchers) is required to authenticate the current user before data can be manually accessed; 3) the web browser application linking the investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption) which will guarantee the data transfer from web browser to the backend database is well protected; and, 4) the backend database is hosted by Microsoft Azure and the University of Oklahoma Health Sciences Center (OUHSC). Azure has been approved by OUHSC risk assessment. The only personnel who have access to the Azure services are the mHealth developers. Study members have access to participant data through specified roles with secure logins and can only access data for their own projects. Azure databases are encrypted. Further, the data associated with the mobile app is encrypted. Azure uses TDE (transparent data encryption) AES_256. The database on the app-related phone is encrypted with SQL-Cipher, which also underwent risk assessment and was approved for use by OUHSC. The OUHSC SSL certification for https encrypts data in transit. They only data that will be downloaded is data that can be accessed by the OUHSC research team. Only research team personnel with specific roles can log in and download data. These steps will ensure the security of EMA data. Software will be downloaded onto each study phone so that phones can be remotely wiped if lost or stolen.
- All research personnel associated with this study will complete the Human Subject Protection Training Program or a training program approved by OUHSC. These are standard procedures used by PI of this application and they have been effective in the past. As a result of these practices, it is unlikely that any loss of privacy will occur during the course of the study.
- A Federal Certificate of Confidentiality is automatically provided by the NIH to protect against disclosures or release of data. All research personnel associated with this study have completed the Human Subject Protection Training Program or a training program approved by OUHSC.

Coercion. Participants will be told at the screening and at the time of consent that their participant is completely voluntary. They will be reminded at each in-person visit, and at the 30-day follow-up that they can decline to answer any question and they can withdraw their participation at any time without penalty. Individuals will be also told at consent and reminded again at each in-person visit that they can decline to continue using the study product at any time, and still remain enrolled

in the study and undergo the study assessments. This will reduce the potential for incentivizing continued smoking. All research team members will complete an approved course on the protection of human subjects and be trained on how to clearly describe study procedures and obtain informed consent.

Discomfort from withdrawal. Participants will be given information about the possibility of nicotine withdrawal symptoms during the phone screening and again at the consent process. Participants will be told that they have the right to drop out of the study at any time. All participants will be informed that smoking and combusted tobacco use is dangerous for one's health, but that the smoking involved in the study poses no more harm than their usual smoking exposure. As noted above, all participants will be given a list of resources to assist them to quit smoking should they be interested and at the completion of the study.

Compensatory smoking and/or other tobacco use. The risk of compensatory smoking or increased use of tobacco products will be minimized by tracking daily cigarette and alternative tobacco product consumption assessed via EMA; and evidence of CO increase beyond acceptable levels (assessed at each in-person visit) will result in withdrawal from the study (see DSMP for further details). To minimize the risk of compensatory smoking or increased use of tobacco products, participants' daily smoking will be monitored for any increase as described in detail in the DSMP, and participants will be withdrawn if a marked increase in smoking or other tobacco use is evident. We note that in a recent trial of VLNC cigarettes in which adult smokers were given access to SPECTRUM cigarettes including VLNC doses for 6 weeks and expected to smoke only those cigarettes, there was no evidence of compensatory smoking, neither as measured by cigarettes per day nor by cotinine or toxicant exposure; therefore, we do not expect compensation to occur. Similarly, as noted above, in Co-I Cassidy's current field trial of these cigarette doses in adolescents, we have not yet seen significant compensation (N=45 complete as of 2/2018); therefore, this outcome is unlikely. However, we will monitor indicators of increased smoking and alternative tobacco as discussed below and in the DSMP. We will work closely with our consultants to determine decision rules regarding removal from the trial and/or resumption of usual brand cigarettes based on the number of daily reported cigarettes and weekly CO levels to ensure that participants' risk is not increased.

Smoking in the laboratory. Smoking a single cigarette in the lab is used to measure potential compensatory smoking, an important issue under study. Risks related to cigarette puffing will be minimized by limiting this procedure to only one cigarette to and individuals who are smoking "somedays" or "everyday" for > the past 3-months who have no desire to quit. The laboratory where sessions will be completed was constructed with a special ventilation system for quickly removing smoke from the experimental rooms to reduce excess smoke exposure to participants and researchers.

According to new federal statutes, individuals under the age of 21 are not legally allowed to purchase tobacco products. The PI has discussed the legality of providing tobacco products to individuals under the age of 21. In accordance with Oklahoma state bill SB319, we are able to provide cigarettes to individuals ages 18-20 in the context of an IRB approved study.

Reduced harm perceptions of VLNCs. The possibility of perceiving a reduced risk of harm with VLNC cigarettes is moderate. At the end of the study, app participants will be debriefed about the relative and absolute risks of all products involved in the study and remind participants that all cigarettes have negative health effects. Participants will also be provided resources to encourage cessation.

3. **Describe potential benefits and importance to the participants and others.**

The participants may benefit directly through increased understanding of factors underlying uptake, appeal, and use of cigarettes or other tobacco products. This study is designed to answer important questions about factors that promote tobacco use behavior with the ultimate goal of informing prevention and regulatory decisions about menthol cigarettes and other flavored tobacco products. Improved regulation could ultimately help deter tobacco use among the larger population of young people, thus decreasing overall rates of tobacco-related morbidity and mortality, including those that stem from tobacco use and dependence.

4. **Discuss why risks are reasonable in relation to benefits.**

The risks are reasonable in relation to the benefits, as the benefits from conducting this study will help inform Food and Drug Administration regulation of menthol flavored cigarettes. Menthol cigarette smoking is linked to smoking initiation among youth and young adults, greater nicotine dependence compared to non-menthol cigarette smoking, and worse smoking cessation outcomes compared to those who smoke non-menthol cigarettes. Menthol cigarettes are also disproportionately used by minority and vulnerable populations, including Black and Hispanic smokers and women. These groups are disproportionately targeted by tobacco company marketing and experience worse tobacco use outcomes. As such, collecting data that would inform a ban on menthol cigarette smoking would significantly improve public health.

**POTENTIAL BENEFITS**

The participants may benefit directly through increased understanding of factors underlying uptake, appeal, and use of cigarettes or other tobacco products. This study is designed to answer important questions about factors that promote tobacco use behavior with the ultimate goal of informing prevention and

regulatory decisions about menthol cigarettes and other flavored tobacco products. Improved regulation could ultimately help deter tobacco use among the larger population of young people, thus decreasing overall rates of tobacco-related morbidity and mortality, including those that stem from tobacco use and dependence.

## J. Statistical Methods

1. **Power**: All assessment methods of this proposal (laboratory, EMA, ETM) are adequately powered to test the primary outcomes of interest. Participants will be n = 100 menthol smokers aged 18-34 years. We will over-recruit for n = 132 to account for a conservative 20% attrition rate over the course of the study; with an estimated final analytic sample size of n = 100. We have specifically accounted for potential study drop-outs, un-enrollments due to changes in eligibility or AE/SAEs, and those who are lost to follow-up in our estimated 20% attrition rate. Attrition rate estimate based on previous studies conducted by Co-Investigators Dr. Donny and Dr. Cassidy, and by consultant Dr. Hatsukami. We based our sample size on effect sizes calculated from similar studies that tested the effect of VLNC cigarettes on adult participants across 6 to 20 weeks of exposure [18, 19]. A sample size of 100 participants would allow us sufficient power (defined as 0.8) to detect differences observed in adult cigarette smokers on the primary outcomes of interest. We will also recruit an additional n = 40 SGM menthol smokers aged 18-34 years with the supplemental funds recently obtained from the NIH. We anticipate that 15% of the parent grant sample will endorse being SGM (n = 15), based on PI Cohn's ongoing data collection efforts; thus, leaving a total sample of n = 55 SGM respondents (inclusive of the supplemental sample)

2. **Laboratory Analyses (Aim 1)**

**Primary Outcomes**: (a) The relative reinforcing value (RRV) of usual brand cigarettes vs menthol VLNCs; (b) RRV of non-menthol VLNCs vs menthol VLNCs. RRV will be operationalized as within-subject differences in subjective ratings of cigarette appeal/reinforcement (satisfaction, reward, craving reduction, physical sensations) during each ad libitum smoking session. Secondary Outcomes: (a) CO boost; and (b) puff topography (number of menthol versus non-menthol cigarette puffs consumed, number of minutes smoked, interval between puffs).

Analysis of covariance will be conducted to examine effects of cigarette type (usual brand, menthol VLNC, non-menthol VLNC) on the outcomes of interest, controlling for cigarettes per day (CPD), nicotine dependence, race/ethnicity, gender, and age of smoking onset as potential covariates. Factors related to study drop-out and differences in cigarette compliance will also be examined as potential covariates. Exploratory analyses will examine differential reactions to usual brand and each research cigarette by race/ethnicity (White, Black, Hispanic, Other) and by gender. Significant interactions will be followed up with individual contrasts of cell means using Fisher's Least Significant Difference tests. We will examine whether topography differs as a function of in-person versus remote session.

3. **EMA Analyses (Aim 2)**

**Primary Outcomes**: (a) within-day subjective response (craving reduction, satisfaction, psychological reward, physical sensations like throat grab) to the most recent cigarette smoked; (b) within-day number of research cigarettes smoked per day; (c) within-day number of non-research cigarettes smoked; and (d) within-day withdrawal intensity. Secondary Outcomes: (a) within-day use of alternative tobacco products; (b) changes over the course of days (creating an average change score for each person) for each outcome; (c) number of days abstinent from tobacco use.

Patterns of missing data, compliance, distributional properties of variables, and correlations among all measures will be assessed. We will control for potential variables related to missing data and utilize multiple imputation methods (expectation maximization algorithm).[160-163] Analysis will use linear mixed modeling with random subjects effects[164,165] to assess the main effect of cigarette type on the primary and secondary outcomes of interest. Models will use a contrast to compare differences between menthol VLNC and non-menthol VLNC at the day-level on predictions of the outcome of interest and that outcome of interest at time t (e.g., morning) predicting behavior (number of cigarettes, any smoking, craving, withdrawal) occurring at a subsequent time point (controlling for cigarette consumption from the previous report). Comparison of usual brand and the menthol VLNC ratings will also be made to determine the perceived similarity of the VLNC to one's own brand. A sub-group of respondents may have fixed (unchanging) ratings of subjective response, craving, cigarettes per day, or withdrawal over the course of 7 days, although this is unlikely given the team's previous research. We will examine baseline and daily factors that set "no changers" apart from those whose show fluctuations in these factors, and examine these as potential covariates in models. Within-person slopes capturing associations between cigarette type and the EMA outcome of interest will be saved in regression models and used to predict the ETM responses.

4. **ETM Analyses (Aim 3)**

**Primary Outcomes**: (a) consumption of alternative tobacco products (milligrams of nicotine for alternative tobacco sources) as a function of cigarette type available. Typically, as cigarette price increases, consumption of other tobacco products increases.14 Secondary Outcomes: (a) breakpoint: the first price at which consumption of the available cigarette is zero; (b) intensity of demand: consumption at the lowest price); (c) elasticity of demand: sensitivity of cigarette consumption to increases in cost, (d) Omax: maximum expenditure for cigarette type available; and (e) Pmax: price at which expenditure is maximized.

The analyses for the aim using ETM data will examine the predictive validity of laboratory and EMA data on the ETM outcomes of interest, separately for each cigarette type. Hierarchical linear regression models will predict the ETM outcome of interest, controlling for baseline cigarettes per day, nicotine dependence, other tobacco use, and relevant demographics in Step 1 and then

including the laboratory or EMA-derived slopes of appeal/reinforcement in Step 2. Models will separately examine the effects of laboratory and EMA measurements of appeal/reinforcement on the ETM outcomes of interest.

5. **Exploratory Analyses**

Differences by age (18-24 vs 25-34), sex, race/ethnicity, alternative tobacco product use, and ETM flavor and product preference. Menthol cigarettes are disproportionately used by women, as well as Black and Hispanic smokers.[18,166-168] As such, sex and race/ethnicity will be examined as moderators of outcomes, as sample size permits. This allows us to adhere to NIH guidance examining sex as a biological variable. Variation in the use of alternative tobacco products during each 7-day take-home phase will be examined as a possible moderator of the reinforcing effects of the research cigarette to which participants are assigned, as well as an outcome assessment of compensatory tobacco use. Given the popularity of menthol cigarette use in adults aged 26-34 years and alternative tobacco product use in this age group,[17,169-171] flavor preference by product type (e-cigarettes, little cigars) will be examined as an exploratory outcome from the ETM analyses.

Laboratory and EMA concordance and predictive utility. We will examine the association of laboratory and EMA measurements of appeal/reinforcement and determine whether correlations between these measures differ in magnitude by menthol vs non-menthol use and by VLNC vs usual brand. A weak or non-significant correlation could indicate that these paradigms tap into different dimensions of reinforcement/appeal. We will also compare the utility of laboratory vs EMA outcomes as predictors of ETM outcomes to determine the relative contribution of each measurement paradigm. This would advance theoretical models and facilitate future research by identifying the most relevant aspects of abuse liability that uniquely account for the role of menthol in increasing risk for dependence.

6. **Study Timeline.**

The methodology, sample, sample size, and recruitment were adequately chosen to complete analyses for primary and secondary outcomes in the 3-year time-frame. Months 1-6 will be used for protocol set-up, applying for and obtaining IRB approval and then SPECTRUM cigarettes, staff training, and survey development. During this protocol set-up phase, we will register the study in ClinicalTrials.gov, certify study compliance, and ensure all project personnel complete the Good Clinical Practice training (if not already completed). To ensure that data collection is sequences with other ongoing studies in the HPRC laboratory and we do not overload study personnel with follow-up assessments and EMA data tracking, data collection will occur over the course of 22 months (months 7-28), with a recruitment rate of ~6 participants per month (1-2 a week). This recruitment goal is feasible given the study team's successful recruitment of smokers in past and on-going studies.[20-26] Per NIH guidelines, the clinical trial will be registered no later than 21 days after the first participant enrolls in the study.

Data cleaning will be ongoing. Development and submission of a protocol manuscript will occur at the end of Year 1. Preliminary statistical analyses will begin in Year 2 (month 13-14) in preparation for an abstract submission to the Tobacco Regulatory Science Program (TRSP) annual conference (abstracts typically due in June of each year), and a "Rapid Response" abstract submission to the Society for Research on Nicotine and Tobacco (SRNT) annual conference (abstracts typically due in December of each year). Development and refinement of study codebooks will begin early in Year 2 to support these conference submissions. Development of main outcomes manuscripts will begin at the end of Year 2 and will be ongoing throughout Year 3 (months 25-36).

## K. Data and Safety Monitoring Plan

The below Data Safety Monitoring Plan has been reviewed and approved by officials at NIH/NIDA.

We will monitor for risks related to cigarette smoking by screening participants via self-report for general medical precautions (cardiovascular disease) at baseline and each in-person study session. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (< 1%) and mild (nausea, headache) and will be handled quickly (i.e., advice to participant to reduce or eliminate cigarette use).

Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, birth defects, and other problems. To avoid risks to the participant and fetus, female participants will be tested for pregnancy at every smoking visit or session. If a participant becomes pregnant during the study, she will be withdrawn from the study.

A Randomization and Product Tracking database will be used in REDCap (the electronic data capture system) to track participants' use of menthol and non-menthol study cigarettes. Randomization of when participants will smoke the menthol and non-menthol study cigarette will be deployed and tracked within REDCap, and presented by the Project Manager in a weekly CONSORT diagram presented at weekly project team meetings.

**Process of Adverse Event (AE)/Serious Adverse Event (SAE) collection,**

While participating in the trial, adverse events, serious adverse events, and changes in medications will be assessed at every study visit and carbon monoxide will be obtained. Medical events will typically be identified during the administration of the **Adverse Events Form** and the Health Changes Questionnaire. Other events may be identified by spontaneous reports during non-scheduled assessments. Participants will also be given an emergency number they can call if necessary.

**No new AE is considered if one or more conditions below are met and the description does not otherwise meet the definition of an AE.**

1) Existing AE already open for reported symptom.
2) Pre-existing condition without increase in severity or frequency of symptoms (brief medical history will be updated if not previously reported).
3) Received preventative or follow-up medical care.
4) Other (as determined by the PI and medical monitor).

**Serious adverse events (SAEs):** Information about all serious adverse events will be collected and recorded on a standard Serious Adverse Event Report Form. To ensure participant safety, each study-related serious adverse event will also be reported to the IRB office within 24 hours and NIDA Program Officer within 72 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:
1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A hospitalization would not be considered to be a serious adverse event if it was elective, pre-planned, or for a pre-existing condition that did not worsen since starting the study; or for treatment on an outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

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

**For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:**
1) Cardiovascular disease (CVD) event: Typically include*s* MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).

3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5) Pregnancy: If a participant indicates she is pregnant or has a positive pregnancy test at any session, she will be withdrawn from the study, and this event will remain open until delivery. At that time the medical monitor will contact the participant to ask a few questions about the baby's health and will update the open 'Adverse Event Form'.

**The following will be monitored and can lead to the participant being withdrawn by the PI or Medical Monitor:**
1) 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 PI and medical monitor to determine whether continued participation in the study is appropriate.
2) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then the PI can withdraw him/her from the study at her discretion.
3) Expired breath carbon monoxide increase: A participant will be withdrawn from the study if the average of two consecutive CO readings during the same visit is 100 ppm or greater.
4) Following Co-I Cassidy's protocol with adolescents (aged 15-19), we will monitor indicators of increased smoking/tobacco use at each in-person visit, as described above. To minimize the risk of compensatory smoking, participants' daily smoking will be monitored via EMA for any increase as described in detail above, and participants will be withdrawn if a marked increase in smoking is evident. Evidence of marked increase in smoking or tobacco use: A participant will be withdrawn from the study if s/he meets the following criteria for two consecutive study visits.

- Expired breath carbon monoxide increase: If during a laboratory session his/her CO measurement is as follows (based on CO measurement at baseline):

i. CO is greater than 50 ppm if CO at Baseline (Visit 1) is <20 ppm.
ii. CO is greater than 60 ppm if CO at Baseline (Visit 1) is 20 – 34 ppm.
iii. CO is greater than 70 ppm if CO at Baseline (Visit 1) is 35 – 49 ppm.
iv. CO is greater than 80 ppm if CO at Baseline (Visit 1) is 50 – 64 ppm.
v. CO is greater than 90 ppm if CO at Baseline (Visit 1) is 65 – 80 ppm

5) At each session, heart rate and blood pressure (or heart rate only if taken remotely) will be taken. Individuals who show heart rate and blood pressure out of range will be rescheduled. A note will be recorded in REDCap if a participant is rescheduled due to out of range score. If a participant shows out of range vitals on two consecutive visits, this will be reviewed by the PI and medical monitor to determine whether continued participation the study is appropriate. Blood pressure acceptable range: SBP <90

or>140mmHg; DBP >90 or<50 mmHg. Heart Rate acceptable range: bpm <49- >100 bpm.

**Desire to Quit Smoking**

We will query about desire to quit smoking at screening, each in-person visit (or virtual session), and at the follow-up. Those who report a desire to quit smoking after study enrollment will be asked if they still want to receive the study cigarettes. This is because use of reduced nicotine cigarettes could help reduce craving and increase the odds of successful smoking cessation among smokers according to findings published by Co-I Cassidy.[27] Individuals will also be told at consent and reminded again at each in-person visit that they can decline to continue using the study cigarettes at any time, and still remain enrolled in the study and undergo the study assessments. This will reduce the potential for incentivizing continued smoking. Those who do not want to continue receiving the study cigarettes will no longer be dispensed study cigarettes and will be retained in the study with no penalty and will continue to complete all subsequent EMAs, the ETM, and the 30-day follow-up. Retaining individuals who have stopped using the study cigarettes, or who report a desire to quit smoking and wish to use VLNCs, are vital to informing the outcomes of the study. All participants will be given smoking cessation resources at their request, upon completion of the in-person/virtual study visits (Visit 5), and again at the 30-day follow-up (in-person or on the phone).

Investigator responsibilities for notification of SAEs are described above. The PI will be available for any questions that participants may have about smoking, or smoking cessation. Participants will be given contact numbers of the laboratory and PI. Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be discussed immediately with the PI (Dr. Cohn). Dr. Cohn, or a delegate (Project Manager) will be responsible for completing an Adverse Events Form should an event occur. The Adverse Events Form will be reviewed by the PI and medical monitor. Dr. Cohn and the medical monitor will gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the OUHSC IRB.

**Trial stopping rules**

The trial will be stopped if the OUHSC IRB recommends trial discontinuation due to SAEs, if the trial is not progressing due to lack of participant recruitment, or if advised by the medical monitor.

**AE/SAE follow up plan**

A participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes or procedures. Any AE that remains open will be reviewed and closed during the 30-day follow-up phone call

**DSM Plan Administration**

**Responsibility for data and safety monitoring**
During study sessions, data will be entered in real-time into a laptop or desktop computer to REDCap and by participants into the CMS, which is the electronic data capture system for the EMA application (which has been approved for use by OUHSC). The study PI (Dr. Cohn) will provide a Data Safety and Monitoring report to NIDA along with each progress report (annually). The PI will be responsible for the oversight of internal monitoring of the participants' safety and data integrity of their project, executing the DSM plan, and complying with the reporting requirements to the local IRB, the FDA, and NIDA.

**Frequency of DSM**
The PI and the research staff will meet weekly throughout the project. During these meetings, the team members will evaluate the progress of the trial, review data quality, recruitment, retention, and examine other factors that may affect study outcomes. The medical monitor will attend these meetings as needed or as requested. They will also review the rates of adverse events to determine if there are any changes in participant risk. The PI is available to meet outside of the scheduled meetings, if concerns regarding a particular participant or another problem should arise. The study PI and Co-Investigators, along with the medical monitor, will meet monthly to review overall progress, and any recruitment, data quality, and safety concerns. Specifically, they will assess enrollment information, demographics and characteristics of the participants, the expected versus actual recruitment rates, quality assurance or regulatory issues that may have occurred during the past month, review a summary of adverse events (AEs) and serious adverse events (SAEs), protocol violations, and any actions or changes to the protocol. The team members will be available to meet outside of the scheduled meetings if concerns regarding any adverse trends or other major problems should arise.

**Content of DSM report**
The DSM report will be submitted to the NIDA Program Official annually. This report will include a brief description of the trial and progress, enrollment information, baseline demographics and characteristics of the participants, the expected versus actual recruitment rates, retention and disposition of study participants (active, completed, terminated/withdrawn), quality assurance or regulatory issues that may have occurred during the year, a summary of adverse events and SAEs, protocol violations/deviations, any actions or changes to the protocol, and any actions by the IRBs.

**DSM Board Plan**
We have not been informed by or requested by NIH/NIDA that we are required to have a DSM Board.

## L. Data Sharing

All data will be utilized in accordance with the standard reporting procedures for

NIH grants and CONSORT (Consolidated Standards of Reporting Trials), an evidence-based, minimum set of recommendations for reporting research findings. There are organizations outside the OUHSC that may inspect and/or copy research records for quality assurance and data analysis. These organizations may include the funding organization of this project (University Hospital Authority Trust) other regulatory agencies. The FDA/NIH, the OUHSC Institutional Review Board, and other University administrative offices may also inspect and/or copy research records for these purposes. Outside of these purposes where identifiable information may be required by the reviewing regulatory agency, all data will be de-identified prior to sharing. Additionally, data may also be de-identified and used in aggregate form. All identifiable information will be destroyed at the end of the study, unless the participant consents to have their info retained in our database so they could be contacted for future studies.

## M. Confidentiality

Efforts will be made to keep personal information confidential. Participants will not be identifiable by name or description in any reports or publications about this study. All research data will be identified only with a unique ID and will be kept separate from personally identifying information, such as name and contact information. Biospecimen data that is collected (breath analysis to determine recency of smoking, pregnancy test) will be not be stored. There are organizations that may inspect and/or copy research records for quality assurance and data analysis. These organizations may include the US Food & Drug Administration and other regulatory agencies, the OUHSC Department of Pediatrics. The OUHSC Human Research Participant Program office, the OUHSC Institutional Review Board, OUHSC Office of Compliance, and other University administrative offices may also inspect and/or copy research records for these purposes.

We will remove direct identifiers from data results and assign a code. The key to this code will be kept separately and only the researcher and approved study personnel for this study will have access to the code. If information is shared with another investigator for research purposes, they will not be able to re-identify participants.

Study data will be stored for a minimum of 7 years, or as additional analyses are needed.

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