Impact of a reduced nicotine standard on young adult appeal for menthol and non-menthol cigarettes

Amy M Cohn, Rachel Cassidy, Rachel Denlinger-Apte, Eric Donny, Andrea C Villanti, Dorothy Hatsukami, Delaney Dunn, Riley Wyatt, Taylor Niznik, Tamar Cohen-Davidyan, Michael Smith, Sarah J Ehlke


ABSTRACT

Introduction The Food and Drug Administration (FDA) announced its intention to reduce the nicotine content in cigarettes as a strategy to promote cessation and reduce smoking-related harm. A low nicotine product standard will apply to all cigarettes on the market, including menthol cigarettes. In December 2021, the FDA approved a modified risk tobacco product application for menthol and non-menthol flavoured very low nicotine cigarettes (VLNCs) from the 22nd Century Group. Notably, experimentation with menthol cigarettes is linked to smoking progression, as well as greater nicotine dependence relative to non-menthol cigarette use. If menthol VLNCs are perceived as more appealing than non-menthol VLNCs, this would indicate that some aspect of menthol may maintain smoking even in the absence of nicotine and FDA’s regulatory authority to ban or restrict the sale of menthol cigarettes should apply to reduced nicotine content of cigarettes. In April 2022, the FDA announced proposed rulemaking to prohibit menthol cigarettes, however it is unclear if a menthol prohibition would apply to VLNCs.

Methods and analysis This study will recruit 172 young adult menthol smokers (with a specific subsample of n=40 sexual and gender minority young adults) and measure appeal for smoking experimental menthol and non-menthol VLNCs, and the impact of proposed product standards on tobacco product purchasing behaviour using an Experimental Tobacco Marketplace. Appeal across product standards will be assessed in a controlled laboratory and using ecological momentary assessment.

Ethics and dissemination The protocol was approved by the University of Oklahoma Health Sciences Center Institutional Review Board (#11865). Findings will examine the effects of a reduced nicotine standard and a menthol ban on young adult smoking and will be disseminated through peer-reviewed journal articles and presentations at scientific conferences.

INTRODUCTION

Background The Food and Drug Administration (FDA) announced its intention to reduce the nicotine content in cigarettes as a strategy to promote cessation and reduce smoking-related harm.1–4 Notably, a low nicotine product standard will apply to all cigarettes on the market, including menthol cigarettes, which account for approximately 35% of the cigarette market share.5 Recent studies show that menthol cigarette smoking has increased in young adults (YAs; defined here as aged 18–24 years), while non-menthol smoking has decreased in this age group.6–7 African-American and Hispanic smokers, as well as sexual gender minority individuals disproportionately use menthol cigarettes, and this preference is even stronger among young adult smokers.8–12 National data show that the majority of YA smokers initiate with a menthol cigarette13 and that menthol cigarettes are the most popular flavoured tobacco product used by YAs.12 14 Experimentation with menthol cigarettes is linked to smoking progression, and greater nicotine dependence relative to...
non-menthol cigarette use.\textsuperscript{6,15–17} If menthol very low nicotine cigarettes (VLNCs) are perceived as more appealing than non-menthol VLNCs, this would indicate that some aspect of menthol may maintain smoking behaviour, even in the absence of nicotine. Results will 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, as well as address unintended consequences (eg, product switching) from both restricting both menthol flavoured cigarettes and normal nicotine content cigarettes. Furthermore, it is unclear whether VLNCs would be exempt from FDA’s proposal for menthol cigarette ban. Findings will help provide detail about the appeal and use of VLNCs in the context of a menthol cigarette ban.

Objectives
This study will recruit a sample of 172 YA ‘someday/ everyday’ menthol smokers to capture YAs, including a specific subsample of \( n = 40 \) sexual or gender minority YAs, given high rates of tobacco use in this group and specifically menthol cigarette smoking.\textsuperscript{10,12,18} The study will measure reinforcement for smoking experimental (SPECTRUM variable nicotine research cigarettes) menthol and non-menthol VLNCs (0.03 mg) and the impact of proposed product standards and policy scenarios on tobacco product purchasing behaviour using a validated Experimental Tobacco Marketplace (ETM).\textsuperscript{19–22} Reinforcement across product standards will be assessed using complimentary measures in a controlled laboratory and using ecological momentary assessment (EMA).

Design
This study consists of five study laboratory visits and three separate periods EMA. After a prescreen/baseline session to confirm eligibility (visit 1), participants will abstain from cigarette smoking and other nicotine for >12 hours (carbon monoxide (CO)-verified ≤6ppm or >50% reduction in CO from baseline) prior to each of four laboratory 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 ad libitum (visit 2), one menthol SPECTRUM VLNC and one non-menthol SPECTRUM VLNC (visits 3 and 4) via the Clinical Research Support System (CReSS, Borgwaldt, Richmond, Virginia, USA), which is a handheld device that measures puff behaviour. The order of menthol and non-menthol SPECTRUM cigarette smoking will be counterbalanced. At each laboratory visit, participants will complete measures of subjective response (eg, smoking satisfaction, craving reduction, psychological reward, sensory effects like throat hit), smoking exposure (CO boost) and behaviour (topography: number of puffs, total time smoked). At the fifth and final laboratory visit, nicotine-deprived participants (≥12 hours) will return to the laboratory to complete two ETM tasks which will assess hypothetical tobacco purchase behaviour in response to two different policy scenarios where (1) a menthol cigarette ban and reduced nicotine standard are present and (2) only a reduced nicotine standard is present (but no menthol ban is present) (more detail below). Participants are contacted 30 days after this final visit to complete an assessment of cigarette smoking and other tobacco use, to determine if smoking has returned to baseline levels or reduced, and to provide cessation resources (table 1).

METHODS: PARTICIPANTS, INTERVENTIONS, OUTCOMES
Study setting
Participants will be recruited from Oklahoma Tobacco Settlement Endowment Trust (TSET) Health Promotion Research Center (HPRC), located in Oklahoma City, using methods that have been used in previous studies by the Principal Investigator (PI): local newspapers (including at local colleges/universities), online (eg, Facebook, Instagram), community flyers, snowball techniques and a database of interested callers from previous and other ongoing smoking studies. Additionally, participants will be recruited through third-party recruitment partners who provide prescreened referral participants for additional screening to determine full eligibility. Men and women of any ethnic or racial group are eligible if they meet inclusion/exclusion criteria. All recruitment materials direct participants to complete an online screening or call the study number to determine eligibility. For print ads, a QR code is included. Recruitment was planned to begin in October 2020, but was delayed due to COVID-19 and the change in the federal and state law that increased the legal purchase age of tobacco products and disallowed the study team from providing tobacco products to individuals aged 18–20 years, as the protocol was originally written. After the study protocol was redesigned for remote and socially distant administration, study recruitment began in September 2021. A new law in Oklahoma was passed in November 2021 that allowed the study personnel to furnish the experimental VLNCs to individuals aged 18–20 years without criminal liability, as per the study protocol.

Eligibility criteria
Inclusion criteria: (1) aged 18–26 years; (2) currently smoke cigarettes ‘somedays’ or ‘everyday’ for at least the past 3 months; (3) strong preference for menthol cigarettes (ie, smoke menthol ≥80% of the time)\textsuperscript{23}; (4) ability to read English at an eighth grade level or higher and (5) no immediate plans to quit smoking. Exclusion criteria: (1) current use of nicotine replacement therapy; (2) pregnant, planning to become pregnant or currently breastfeeding (verified by pregnancy test at each study visit/virtual smoking session; (3) past or current self-reported clinically significant heart disease or hypertension, or other smoking-related disease (by history) that preclude successful study completion; (4) serious psychiatric disorder; (5) inability to abstain from nicotine/tobacco products and caffeine prior to study visits; (6)
strong preference for non-menthol cigarettes (smoke non-menthol >80% of the time).

Interventions

Eligible participants will be provided both menthol and non-menthol SPECTRUM research cigarettes to take home and smoke for 7 days. At the end of each 7-day ‘take home’ period, participants will return to the laboratory to smoke that cigarette flavour in laboratory. The order of administration for dispensing the menthol and non-menthol cigarettes is randomly generated using a block randomisation process with a block size of 4. This process ensures that the samples will be balanced across dispensing order (ie, menthol in the first ‘take home’ period vs second) over time. Menthol and non-menthol VLNCs are provided by the National Institute on Drug Abuse (NIDA) through the NIDA Drug Supply Programme.

Outcomes

Primary outcome measures: (1) change in puff topography—total inhalation volume from smoking behaviour in the laboratory; (2) change in cigarette evaluation scale (CES)—subjective response to smoking; (3) hypothetical purchasing of tobacco products—purchasing cigarettes and other tobacco products across changing prices in ETM task. Secondary outcome measures: (1) change in CO boost—measures expired alveolar CO level; (2) drop-out rate—measure of compliance; (3) Minnesota Nicotine Withdrawal Scale (MNWS)—measures withdrawal symptoms; (4) Questionnaire on Smoking Urges (QSU)—measures craving; (5) Positive and Negative Affect Scale (PANAS)—measures affect; (6) Perceived Health Risk Scale—measures perceptions of risk of smoking; (7) heart rate—measures cardiovascular function; (8) blood pressure—measures cardiovascular function assessed through both systolic and diastolic pressures.

Participant timeline

Study eligibility will be confirmed via an in-person/screening visit (visit 1), by a trained research technician. Individuals who are eligible at visit 1 will be asked to consent and then complete the baseline questionnaire of tobacco use behaviour, tobacco use history, perceptions of tobacco use and other health behaviours related to tobacco use (eg, alcohol use, cannabis use). After visit 1, participants will be asked to engage in a 7-day baseline period of usual brand smoking at home, where they will be asked to record cigarette and other tobacco use, subjective response to smoking, craving and withdrawal, via twice-daily EMA. At the end of the 7 days, participants will be asked to return to the laboratory for visit 2 (smoking session 1), to assess reinforcement of one’s
usual brand cigarette smoking via ad libitum smoking in the laboratory. Following visit 2, 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 brand cigarette for the assigned cigarette for each 7-day period (allowing for other tobacco product use during that time without specific instruction, to model real-world behaviour). Each condition will be separated by a 7-day washout period. On the last day of each condition (smoking visits 3 and 4), participants will smoke the assigned research cigarette ad libitum in the laboratory, and data on subjective response, smoking exposure and behaviour will be measured. During each 7-day period, participants will complete assessments of cigarette and other tobacco use, withdrawal and subjective response (satisfaction, craving reduction, reward, sensory effects) via twice-daily EMA. At visit 5, participants will complete two ETMs in the laboratory to model the impact of menthol flavouring 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 versus non-menthol VLNCs at increasing prices under the scenario where a nicotine reduction policy is in effect but menthol in combustible cigarettes is available. Finally, participants will complete a follow-up assessment 30 days after smoking visits 3 and 4 to assess return to baseline smoking and other tobacco use, reactivity (eg, behaviour change) to EMA surveys and will be provided cessation referrals. It is anticipated that the study timeline for each participant will take approximately 2 months.

Methods for addressing COVID-19 restrictions
In response to university social distance, masking and closure policies, the order in which study phases can occur may differ in response to the COVID-19 virus. Participants will be offered socially distanced in-person visits or remote study sessions, at their choice. Online informed consent and baseline survey will be offered. Once consent is obtained, and the baseline survey is complete, a participant will have the option to complete the study via remote study sessions. Participants who complete the study remotely will be given a smartphone compatible portable CO monitor (Bedfont iCO Smokerlyzer) and asked to use the iCO reading to verify smoking status at the beginning of each remote smoking session and exhaled CO (exposure) following smoking. Each participant will be provided their own iCO Smokerlyzer free of charge. Remote smoking sessions will occur via Zoom video. The mode of study sessions (remote vs in-person) will be coded and examined as a potential covariate in final analytic models.

Sample size
All assessment methods of this proposal (laboratory, EMA, ETM) are adequately powered to test the primary outcomes of interest. Participants will be n=140 menthol YA smokers (inclusive of the parent grant and supplemental grant). We will over-recruit in the parent grant (n=32) to account for a conservative 20% attrition rate over the course of the study, with an estimated final analytic sample size of n=100 for the parent grant and n=40 for the supplemental grant. We have specifically accounted for potential study drop-outs, unenrolments due to changes in eligibility or adverse events/serious adverse events and those who are lost to follow-up in our estimated 20% attrition rate. We based our sample size on effect sizes calculated from similar studies that tested the effect of VLNC cigarettes on adult participants across 6–20 weeks of exposure.24 25 A sample size of 140 participants would allow us sufficient power (defined as 0.8) to detect differences observed in adult cigarette smokers on the primary outcomes of interest.

Recruitment
Recruitment and enrolment will occur at the laboratory of the TSET HPRC, in Oklahoma City, Oklahoma, which is specifically designed for the observation and measurement of cigarette smoking and tobacco use behaviour. The team will use methods that have been successfully in previous studies: local newspapers (including at local colleges/universities), online (eg, Facebook; Instagram; Snapchat; YouTube; TikTok), community flyers, snowball techniques and our database of interested callers from previous and ongoing smoking studies. The laboratory’s close proximity (<10–20 miles) to several colleges and universities will further aid in our ability to recruit the sample of YAs.

Planned start date: October 2020
Planned end date: April 2023

METHODS: ASSIGNMENT OF INTERVENTIONS (FOR CONTROLLED TRIALS)
Not applicable; this is not a controlled trial.

METHODS: DATA COLLECTION, MANAGEMENT, ANALYSIS
Data collection methods
Measures
The following domains will be assessed: (1) demographics; (2) tobacco use patterns (age at first use; nicotine dependence (time-to-first use from the modified version of the Fagerstrom Tolerance Questionnaire (mTFQ)),26 cigarettes per day (CPD); alternative tobacco product use; motivation to quit and quit history; peer tobacco use; tobacco marketing/media exposure 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) cultural identification and experiences
of discrimination; (7) delayed discounting and (8) factors associated with tobacco use (stress, alcohol, marijuana, drug use). Positive and negative characteristics of cigarette smoking will also be measured. 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.

Respiratory symptoms will be assessed using the American Thoracic Society Questionnaire (ATSQ).27 28 Participants report the frequency of experiencing each of eight respiratory symptoms (eg, 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)29 will be used to evaluate suicide risk. A licensed clinical practitioner will be available to conduct the mental health assessment. 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)30 31 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. A brief medical history form designed specifically for this study will assess physical and emotional health to establish eligibility for participation. In subsequent sessions, the Health Changes Questionnaire, also designed specifically for this study, 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 General 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 visit 2 (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.32 34 The TLFB will determine: number of CPD; 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. Second, the 7-day Tobacco Use Questionnaire will be administered at VLNC2 pick-up (between visits 3 and 4), where there is a 7-day washout 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),35 36 a behavioural economics-based measure of cigarette reinforcement, which assesses hypothetical demand for cigarettes across a range of prices, and a cross-price elasticity purchase task,37 which assesses hypothetical demand for experimental cigarettes at increasing prices of an individual’s preferred brand of cigarettes. The CPT38 39 will be used to assess demand for both their usual brand cigarette which may change as a function of VLNC exposure. Participants will be asked how many cigarettes of their usual brand and their study cigarette they would purchase at increasing costs per pack, starting with how many they would consume when cigarettes are free (zero price). This measure has been validated for use in adolescents.40 Participants will be instructed to imagine their own brand of cigarette at visit 2 and the assigned VLNC they have smoked at subsequent visits. Participants will also complete assessment of nicotine withdrawal and craving prior to smoking using the MNWS40 and the QSU,42 respectively. 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),43–45 the Duke Sensory Questionnaire (DSQ)46 and the Nicotine Drug Effects Questionnaire (NDEQ).47 Participants will also complete the MNWS again. The mCEQ measures subjective responses smoking in five dimensions: psychological reward, satisfaction, aversion, craving reduction and throat hit (eg, sensations in the mouth and throat). The DSQ assesses puff liking and satisfaction; nicotine in puffs; similarity to own brand and puff strength on the tongue, nose, mouth. Items are summed to measure cigarette liking and somatic sensation. The NDEQ measures subjective experience to nicotine as a function of strength of the nicotine ingested and desirability of nicotine’s effects.

The Predicted Behaviour Questionnaire will be asked at the beginning of visits 3 and 4, prior to when each VLNC is smoked. This questionnaire asks participants to indicate their intentions to use cigarettes and other tobacco products when cigarettes have lower nicotine content and some menthol or non-menthol flavour. 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), whether they perceive the study cigarettes would help them quit, whether the study cigarette are less dangerous than smoking, whether the study cigarettes would help them give up tobacco use and if they would help them smoke fewer cigarettes.

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.\textsuperscript{46} Items assess tar levels, addictiveness, likelihood to cause cancer, chemical content, overall healthiness and utility for quitting.

Biomarkers

Expired breath CO level is a reliable and valid instrument of recent smoking and will be measured using a Bedfont Smokerlyzer CO Monitor. CO will be assessed at BL to confirm smoking status and for sample description. CO will be evaluated pre-cigarette and post-cigarette in each lab session, and as an outcome as a biomarker of changes in effects of reduced nicotine intake over time.

After a brief screening over the phone, individuals will be provided with a description of the study and procedures. Those who appear qualified and interested will be scheduled for a baseline prescreening session (visit 1).

**PROCEDURE**

**Laboratory visits**

**Visit 1: in-person screening and baseline**

On arrival to the screening/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, he or she 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 PHQ-9 and the MINI suicidal scale to determine evidence of a severe psychiatric disorder. Eligible participants will then complete the baseline surveys. 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 brief 10–15 min training. For 7 days following visit 1 (if eligible), participants will smoke their usual brand cigarette in their home environment, as per usual, and measurements of CPD, craving, symptoms of nicotine withdrawal, subjective response, positive and negative affect and alternative tobacco use will be assessed twice daily via EMA.

**Visit 2: 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) 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. Participants will also be asked to abstain from caffeine for at least 1 hour prior to the session. The instrument records puff volume, duration and velocity and interpuff interval for each puff and their aggregate averages. Prior to smoking, participants will complete the perceived health risks questionnaire (developed specifically for this study) to assess perceived risk for smoking their usual brand of cigarettes, a CPT\textsuperscript{45,46} for their usual brand of cigarettes and the ATSQ\textsuperscript{48} to assess respiratory symptoms. 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 CO boost. Additionally, participants will complete the QSU and MNWS surveys prior to smoking. Subjective response to smoking (craving reduction, psychological reward, satisfaction, sensory effects) using the mCEQ\textsuperscript{45,46} in addition to the N-DEQ\textsuperscript{45} and the MNWS\textsuperscript{46,49} will be measured immediately after smoking. Exhaled CO will be collected via a Smokerlyzer CO detector (Bedfont Scientific), and measured in ppm immediately before and 10 min after smoking as an index of smoke exposure, and will be calculated as the difference between presmoking and postsmitting levels.

At the end of visit 2, participants will receive the first set of assigned research cigarettes (either menthol or non-menthol VLNCs) and asked to smoke those cigarettes in their home environment for 7 days. The ordering of flavour 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 VLNCs. 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 via smartphone. No penalties are provided to participants for smoking their usual brand cigarette, as use of the VLNCs, relative to usual brand cigarettes, will be assessed as an outcome. 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. Participants will have a 7-day period washout period of return to smoking as usual (own brand of cigarette) between the experimental conditions.

**Visits 3 and 4: experimental cigarette smoking**

Study visits 3 and 4 will be identical to each other. Participants will return to the laboratory for visit 3 and visit 4 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 ≤60 ppm or >50% reduction in CO from baseline) and caffeine for 1 hour. Before smoking the assigned research cigarette, participants will complete a CPT, a behavioural economics-based measure of cigarette reinforcement, which assesses hypothetical demand for cigarettes across a range of prices, and a cross-price elasticity purchase task\(^{27}\), which assesses hypothetical demand for experimental cigarettes at increasing prices of an individual’s preferred brand of cigarettes, and a demand for one’s usual brand cigarettes at increasing prices of the experimental cigarettes (separately for menthol and non-menthol cigarettes). Participants will also complete a several attitudinal measures to assess perceived health risk for the study cigarettes and expected utility of smoking VLNCs, the ATSQ to assess respiratory symptoms, the QSU to assess smoking urges, the MNWS to assess withdrawal symptoms and measurements of 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 mCEQ, the N-DEQ, the DSQ and the MNWS. At the end of visit 4, participants will complete a brief survey of satisfaction with and reactivity to EMA and the laboratory portions of the study, to determine if smoking sessions and/or daily monitoring may have impacted their behaviour or perceptions of smoking.

**Visit 5: experimental tobacco marketplace**

Participants will complete the ATSQ, mFTQ, MNWS and QSU after which two separate ETM tasks (counterbalanced) will be administered to >12 hours 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 a week. Participants will receive account balances approximately equal to the money they spend on tobacco in 1 week, which is determined at the baseline visit.

They will be instructed that they can ‘save’ unspent money, and purchase as many or as few tobacco products as their account balance allows, including no tobacco products at all. The price of cigarettes will increase over eight trials (US$0.12, US$0.25, US$0.50, US$1.00, US$2.00, US$4.00, US$8.00 and US$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 (eg, menthol normal nicotine cigarettes (NNCs); menthol VLNCs); this will model a scenario where a nicotine reduction policy is in effect and menthol in combustible cigarettes is banned. 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 (eg, NNCs) are available. 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 flavours, including menthol, to simulate the real-world marketplace. This will model a scenario where a nicotine reduction product standard is in place but menthol is not banned.

Results of the ETM will not be actualised—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.

**30-Day follow-up**

A month (30 days) after the final study visit, participants will complete a brief assessment to determine whether smoking and other tobacco use has returned to baseline levels, and to provide cessation referrals. The smoking stages of change, mFTQ and ATSQ will be administered. This 30-day follow-up will be offered face-to-face or remotely, at the participant’s preference. All participants will also be provided cessation referrals.

**Product dispensing**

At the end of visit 2, participants will be dispensed the first of study VLNC cigarettes (either menthol or non-menthol) to smoke at home for 7 days. Remote participants will visit the study site or meet a team member at a public place in the community to help reduce the burden of travel time and study attrition. Participants will be given enough cigarettes to accommodate usual smoking patterns until the next visit in 7 days (125% of their baseline CPD, based on the team’s previous work). At visit 2, 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 (number of own cigarettes smoked per day×125%×7 days). At each in-person visit or remote smoking session, research staff will complete a ‘Product Accountability Log’ with participants to record
used and unused cigarettes. Remote participants will return study cigarettes (used and unused) at the next curbside pickup/drop-off; used and unused cigarettes will be reviewed with the participant via Zoom or other university-approved video conference platform. 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 want the study cigarettes, 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 session and the 30-day follow-up.

**Product compliance and accountability**

To reduce distribution, hoarding and/or overconsumption, participants will also receive a nominal payment for returning unused cigarettes (US$0.25/cigarette, US$20 maximum per participant). Participants will be instructed to return all unused cigarettes and empty cigarette packs to the laboratory each week. At study visits 3 and 4, 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 labelled with their study ID number and calendar dates; a single plastic storage bag will be used to collect the butts for each smoking period. The payment schedule for returning smoked research cigarettes at each in-person visit (in the form of used butts) is as follows: 75%–100%, US$7; 50%–74% returned, US$5; 25%–49% returned, US$2.50 and 0%–24% returned, US$0. The payment schedule for returning empty cigarette packs at each in-person visit is US$1 per pack (US$5 maximum per participant).

**ECOLOGICAL MOMENTARY ASSESSMENT**

**EMA procedure**

Participants will record cigarette smoking and alternative tobacco use, craving, symptoms of withdrawal and subjective ratings (eg, satisfaction, reward, craving reduction, physical sensations like throat hit) associated with smoking the most recent cigarette in response to two 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. We will use an adaptive random prompting schedule that is programmed to coincide with the participant's sleep-wake cycle (eg, 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 on receiving a prompt (vibration or 'ping') to their phone by touching the screen. EMA entries are expected to last ~5 min will be date-stamped and time-stamped, and recorded immediately. To enhance compliance, we will provide detailed training on EMA and monetary incentives. Prepaid phones or reimbursement for cellular service will be provided (at the participant’s choosing). Prepaid phones will be labelled ‘government property’.

**EMA measures**

EMA measurements will parallel the constructs used in the laboratory assessments (eg, craving, subjective response) and have established psychometric properties. Subjective ratings will be queried using items from the CES. Questions will also assess the use of alternative tobacco products since the previous assessment, characterising flavours (eg, fruit, chocolate), use of usual brand cigarettes, craving, withdrawal and factors associated with smoking (mood, peer use, alcohol, flavoured tobacco use). To minimise response burden, EMA will prompt use-relevant probes via skip patterns. Missed EMA assessments will be retrospectively assessed by phone or online via REDCap survey and noted as such.

**Randomisation procedure**

A Product Tracking database will be used in RedCap (the electronic data capture system) to track participants’ use of menthol and non-menthol study cigarettes. Randomisation of when participants will smoke the menthol and non-menthol study cigarette will be deployed using independent randomisation schemes generated with a block size of 4. The independent randomisation schemes ensure that samples remain balanced across groups (flavour assignment) over time. Each cigarette flavour assignment requiring randomisation uses a different seed value to ensure that the order is different for each scheme created.

**Study debriefing**

At the end of the visit 5 session, participants will be debriefed. Health risk information will be presented for combusted cigarettes, e-cigarettes and other tobacco products, using a handout drawn from CDC Fact Sheet. Participants will also be given a list of cessation resources.

**Retention**

Participants are compensated using an incentive paradigm to ensure participant retention in all five study sessions and completion of all daily EMA surveys. Participants receive US$35 for completing the baseline session. Participants will receive US$45 for completing each in-person laboratory smoking visit (visits 2–4) and US$50 for completing the final in-person ETM session (visit 5). Participants who attend the baseline session but are determined ineligible during that session will receive US$25. Participants will be compensated for completing the daily surveys as follows: they will receive US$1 for each completed EMA survey (totaling US$42), a US$10 bonus each week of EMA for completing all EMA surveys in that 1-week period (totaling US$50) and a US$45 bonus if they complete 85% of EMA surveys over the course of 3 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 behaviour change to daily monitoring, for which they will be paid US$45. Participants who refer an individual who is eligible and who signs informed consent to participate will receive a US$20 referral bonus (limited to one per participant) and those who complete all phases of the study will be eligible for a US$70 bonus.

Participants will receive a nominal incentive for returning unused cigarettes, to ensure that participants do not hoard, stockpile or share cigarettes with others. The compensation schedule for returning unused cigarettes is US$0.25 per cigarette, up to US$20 per participant; and US$1 for returning empty packs, for up to US$5 per participant. For returning used and unused cigarettes at visits 2 and 3, participants will be compensated as follows: 75%–100% returned, US$7; 50%–74% returned, US$5; 25%–49% returned, US$2.50 and 0%–25% returned, US$0.

Participants will receive US$10 for travel for each in person visit (at four visits) or US$10 for each curbside pick-up/drop-off of study cigarettes or other project materials (eg, study phone), for a total of up to US$40. Curbside pick-up/drop-off can be at the HPRC laboratory location or at another public (eg, coffee shop, restaurant, convenience store or shopping centre) agreed on location. Total possible compensation will be US$551.

**Data management**

Data will be acquired through self-report questionnaires, biochemical measures, laboratory smoking and choice procedures. Smoking topography data will be collected in real time during smoking through a mouthpiece of CreSS, a transducer-based smoking topography data collection device. These data will be collected in electronic files coded with participant identification number. Exhaled CO will be collected via Bedfont Smokerlyzer CO detector, and measured in ppm.

For clinical trial data collection, the research facility uses an electronic data capture system to maintain 21 CFR Part 11 compliance and Good Clinical Practice (GCP) standards. The research staff members are responsible for collecting and recording all data, ensuring all fields are completed appropriately, and all corrections are done according to GCP.

The PI will be responsible for overseeing and completing the monitoring process for the research. The research staff members are responsible for collecting and recording all data. Any inconsistencies/deviations from the study protocol will be documented. Staff training will consist of an explanation of the protocol and review of the study surveys and participant record forms, as well as ‘live’ trainings with study participants, regular meetings with team members and the PI and completing the university-approved training in the protection of human subjects. In addition, the duties of each staff person will be outlined and all applicable regulations will be reviewed and questions will be answered. Senior personnel will supervise junior staff and provide re-training in the study protocol as needed.

**Statistical methods**

**Laboratory analysis (aim 1)**

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 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.

**EMA analysis (aim 2)**

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 use multiple imputation methods (expectation maximisation algorithm). Analysis will use linear mixed modelling with random subjects effects 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 (eg, morning) predicting behaviour (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 subgroup of respondents may have fixed (unchanging) ratings of subjective response, craving, CPD 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.

**ETM analysis (aim 3)**

The analyses for the aim using ETM data will compare the results of ETM 1 with ETM 2, where consumption of alternative tobacco products is expected to vary as a function of different cigarette types available and as cigarette prices increases. Analyses will also 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 CPD, 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.

All analyses will control for the potential impact of remote/virtual study administration on the outcomes of interest.

METHODS: MONITORING
Data monitoring

During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the PI and study personnel, who will also review potential adverse events. Team members meet weekly with the PI and discuss enrolment, consent, eligibility, adherence to/compliance with EMA and data collection. If a female participant becomes pregnant during the laboratory smoking phases of the study, she will be immediately withdrawn from the study. All adverse events and serious adverse events will be documented and recorded in accordance with the University of Oklahoma Health Sciences Center (OUHSC) and National Institutes of Health (NIH) policies. This information will, in turn, be reported immediately to all necessary regulatory committees. Any serious adverse event will be reported to the Institutional Review Board and the NIH Project Officer within 48 hours of occurrence. At each study visit, the participant will be directly asked about adverse events that may have occurred, and during the visit participants will be monitored for any adverse effects associated with their cigarette smoking. An annual report summarising all adverse events will also be submitted. Drop-out rates and reasons for dropout will also be monitored to ensure the integrity of the study protocol.

Harms

Participants will not be exposed to any more risk than the usual risk they expose themselves to by choosing to smoke. Questionnaires, smoking topography and CO measurement are all non-invasive and involve minimal risk to study participants. Potential risks to participants include: (1) risk of using cigarettes, (2) loss of confidentiality or privacy and (3) potential discomfort from being asked to abstain from nicotine. The laboratory where visits 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. Smoking cessation resources will be available to all participants at completion of the study, or earlier if requested, and participants will be provided with a list of cessation resources including the Oklahoma Helpline, a free, 24/7, telephone-based resource to provide tobacco cessation counselling. A Federal Certificate of Confidentiality is automatically provided by the NIH to protect against disclosures or release of data.

Auditing

Not available.

ETHICS AND DISSEMINATION
Research ethics approval

This protocol and the informed consent contained in online supplemental appendix 1 has been reviewed and approved by the OUHSC IRB (IRB #11865) with respect to compliance with applicable research and human subjects regulations (see online supplemental appendix 1 for IRB-approved consent). An annual continuing review is required, which includes the total number of participants enrolled and any reports of adverse and/or serious adverse events, as well protocol deviations.

Protocol modifications

Any modifications to the protocol that may impact the conduct of the study, potential benefit of the participant or safety of the participant, including changes in the study objectives, study design, participant population, sample size, study procedures or significant administrative aspects will require a protocol modification to the IRB. Such modification will be approved by the OUHSC IRB prior to implementation. Administrative changes to the protocol that may have no effect on the way the study is conducted or on participant safety or benefit may be approved administratively.

Consent or assent

Informed consent is obtained from each individual prior to participation in the study. All participants are informed that they may withdraw from the study at any time without penalty and will be paid for what they have completed up to that point.

If recruited during university normal operating procedures (when in-person data collection is allowed), eligible participants will provide written consent in person, before they complete the baseline survey. This will take place in the lab. Trained staff will go over 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.

To provide consent electronically, participants will be sent a link to the electronic information consent (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, he or she will be given the opportunity to sign the consent and the research team member will sign as a witness (if the consent is completed in-person). 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.

Confidentiality
All research data will be labelled using numerical codes. All data are managed and analysed onsite by project staff; no transmission of identifiable data outside of research centre will occur. Research data without identifiers will be maintained in a locked file cabinet or on a password-protected server, which can only be accessed by approved study personnel. Paper-pencil versions of study consents or data collection form and will be stored in a locked filing cabinet; electronic versions of consent forms will be stored on a secure server that can only be accessed by approved personnel. Consent forms with participant name do not contain any research data or study ID, and cannot be linked to participant’s research data. Controlled user access to database systems will ensure that only appropriate and authorised personnel are able to view, access and modify study data. All records that contain names or other personal identifiers that link participant ID numbers will be kept on a password-protected server, which can only be accessed by approved study personnel. This information will be used for payment and contact purposes only. Participants’ study information will not be released outside of the study without the written permission of the participant, except as is necessary by any relevant monitoring or regulatory authorities.

Declaration of interests
There are no conflicts of interest to report.

Access to data
The PI and approved team members will have access to the datasets. To ensure confidentiality, data dispersed to project team members who are not employed at OUHSC will be de-identified and not contain any identifying participant information, unless necessary for data analysis.

Ancillary and post-trial care
Smoking cessation resources will be available to all participants at completion of the study, or earlier if requested, and participants will be provided with a list of cessation resources including the Oklahoma Tobacco Helpline, a free, 24/7, telephone-based resource to provide tobacco cessation counselling.

Dissemination policy
Trial results
The sponsor and PI are committed to the open and timely dissemination of research outcomes. Manuscript and conference submissions to peer-reviewed outlets, focused on the primary and secondary outcomes, will assist with the dissemination of results from this study and will provide a critical empirical foundation to support FDA’s proposed regulatory actions to ban or restrict menthol in cigarettes. Results of the study will be reported in ClinicalTrials.gov to increase availability of information to the public and ensure that study results occur in a timely manner.

Authorship
Topics suggested for presentation or publication will be circulated among the team members. We will follow the recommendations set forth by the International Committee of Medical Journal Editors for defining the roles of authors and contributors in publications or presentations that arise from the data.

Reproducible research/Data sharing statement
Investigators in the proposed activity recognise that promising new methods, technologies, strategies or computer software may arise during the course of the research. The study team is aware of and agrees to abide by the principles for sharing research resources as described by NIH in ‘Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources’. While the investigators expect that research tools will be freely shared with the research community, opportunities for technology transfer and translational research will be explored as appropriate. Any data shared will be de-identified and follow the regulations set forth in the university’s applicable human subjects protection guidelines. NIH policy expects that grant recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. The investigators on this grant are committed fully to the principles of research resource sharing through publications, presentations, web sites, direct PI contact and other means as possible.
Data are sensitive, and the priority in sharing data will be protecting study participants’ privacy. This will not be a public use dataset. Data will be available for certain types of sharing in accordance with the terms of a data-sharing agreement and only after the publication of major findings of the study. Only researchers certified in the protection of human subjects will be considered for access to the data.

Data availability
Data are sensitive, and the priority in sharing data will be protecting study participants’ privacy. This will not be a public use dataset. Data will be available for certain types of sharing in accordance with the terms of a data-sharing agreement and only after the publication of major findings of the study. Only researchers certified in the protection of human subjects will be considered for access to the data.

Patient and public involvement statement
There was no active involvement of patients of the public in the development of this research. Patient and public involvement in this grant funded research was not feasible, given the timeline for project submission and the timeline and budget constraints of the funding mechanism.

APPENDICES
Informed consent (see online supplemental appendix 1).

Biological specimens
Not available.

Study status
Study recruitment began September 2021 and is ongoing. The target sample size is 172 (inclusive of the parent grant and supplemental grant). At the time of this submission (August 2022), 261 individuals have been screened for the study; 44 have consented (10 were ineligible at the baseline/screening visit), 34 completed the baseline survey and started study sessions; 16 have completed all laboratory sessions, and 13 have completed the 30-day follow-up.

Author affiliations
1Department of Pediatrics, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
2TSET Health Promotion Research Center, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
3Center for Alcohol & Addiction Studies, Brown University, Providence, Rhode Island, USA
4Social Sciences and Health Policy, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA
5Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA
6Health Behavior, Society & Policy, Department of Health Behavior, Rutgers Center for Tobacco Studies, School of Public Health, Rutgers University, New Brunswick, New Jersey, USA
7Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota, USA
8Department of Psychology, Old Dominion University, Norfolk, Virginia, USA
9Department of Psychology, Old Dominion University, Norfolk, Virginia, USA
10Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota, USA
11Department of Health Behavior, Society & Policy, Department of Health Behavior, Rutgers Center for Tobacco Studies, School of Public Health, Rutgers University, New Brunswick, New Jersey, USA
12Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota, USA
13Department of Health Behavior, Society & Policy, Department of Health Behavior, Rutgers Center for Tobacco Studies, School of Public Health, Rutgers University, New Brunswick, New Jersey, USA
14Health Behavior, Society & Policy, Department of Health Behavior, Rutgers Center for Tobacco Studies, School of Public Health, Rutgers University, New Brunswick, New Jersey, USA
15Department of Psychology, Old Dominion University, Norfolk, Virginia, USA
16Department of Pediatrics, The University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
17Department of Psychology, Old Dominion University, Norfolk, Virginia, USA

Contributors
AMC conceived of the study, AMC, RC, RD-A, ED, ACV and DH initiated the study design and DD, RW, TC-D, TN, MS and SJE helped with implementation. MS, TN, TC-D, RW, and SJE contributed to data acquisition and protocol development. All authors contributed to the review of this manuscript and provided comments. All authors read and approved the final manuscript. AMC is the primary grant holder.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material
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ORCID iDs
Amy M Cohn http://orcid.org/0000-0001-9034-4293
Andrea C Villanti http://orcid.org/0000-0003-3104-966X

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OUHSC Consent Form Instructions Page

Consent Form to Participate in a Research Study
University of Oklahoma Health Sciences Center (OUHSC)

Study Title: Cigarette Smoking in Young Adults

Sponsor: National Institute on Drug Abuse/Food and Drug Administration Center for Tobacco Products (CTP)

Principal Investigator: Amy M. Cohn, PhD
Phone Number: 405-271-1903

KEY INFORMATION ABOUT THE RESEARCH STUDY

You are being asked to participate in a research study. Research studies are voluntary and include only people who choose to take part. This consent form begins with a ‘Key Information’ section to provide important information to help you decide whether or not to participate in this study. More detailed information is provided after the key information. Please take your time, discuss this with family and friends, and ask the investigator and study team any questions you may have.

WHY HAVE I BEEN ASKED TO PARTICIPATE IN THIS STUDY?
You are being asked to participate in this research study because you are a current smoker and meet study eligibility criteria. This study is not going to ask you to quit smoking. This study is being conducted by the University of Oklahoma Health Sciences Center and is funded by the National Institutes of Health (NIH) and the FDA Center for Tobacco Products. Joining the study is voluntary. You do not have to answer any questions that make you feel uncomfortable. You can stop participating or answering questions at any time.

WHY IS THIS STUDY BEING DONE AND HOW LONG WILL IT LAST?
The purpose of this study is to understand how people will smoke very low nicotine cigarettes (VLNCs). We are interested in how smoking these cigarettes affects your smoking, how you feel, and attitudes about different types of VLNCs. We think that you will be in the study for about 2 months.

WHAT WILL I BE ASKED TO DO IN THIS STUDY?
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.

If you agree to participate and are found eligible, you will be asked to do the following:

- Attend 1 pre-screen/baseline assessment visit in our laboratory (or virtually) which may last up to 1 hour. During this visit you will complete medical history questionnaires and complete a series of web-based surveys on your health and smoking behaviors to determine your eligibility in the study.
- Attend 3 experimental visits in our laboratory (or virtually), which may last up to 2 hours each, where you will smoke a cigarette.
- You will be asked to refrain from cigarette smoking or using other nicotine products for at least 12 hours before each smoking visit. We will also ask you not to drink any coffee, soda, or energy drinks for an hour before each visit.
• If you are eligible, you will be asked to smoke your usual brand of cigarettes at home for 7-days and then once in the laboratory.
• You will also be asked to smoke menthol flavored and traditional tobacco flavored research cigarettes in your home environment for 7 days each, and then once in the laboratory. These research cigarettes contain less nicotine than a normal cigarette. The order in which we ask you to use the menthol or non-menthol (tobacco flavored) research cigarettes will be determined randomly.
• You will provide breath samples at the beginning of each smoking visit (or virtual session) to measure when you last smoked.
• We will also ask you to sign a document confirming you have not smoked for the last 12 hours and haven’t had any caffeine in the last hour before each smoking session. If you complete your sessions remotely, we will confirm this with you verbally over the phone.
• For each of the 7-day “take home” smoking period, you will complete daily surveys about your mood and smoking behavior on a phone, two random times a day.
• If you prefer not to use your personal phone or if your personal phone is not compatible with the application that we use for the daily cell phone surveys (Android compatible), we will give you a study phone. You will have to return this phone at the end of the study in order to receive the full amount of compensation you have earned. We will provide only 1 replacement phone per participant, at no cost to you. If you lose or misplace your phone more than 1 time, you may be withdrawn from the study.
• When you smoke in the laboratory (or remotely), you will smoke one cigarette through a machine that measures smoking. You will complete questionnaires about your behavior and mood, both before and after smoking. We will also measure your heart rate and blood pressure before and after smoking and take another breath sample. (We will not be able to measure blood pressure for virtual/remote visits).
• In the final experimental session, you will complete a computerized task. This task will ask you how much you are willing to pay and use different amounts of cigarettes and other tobacco products. This visit will may take up to 1 hour to complete. You will have the option to purchase no tobacco products at all in this computerized task.
• Finally, 30-days after your final study visit, you will complete a brief survey (on the telephone or in-person) about your tobacco use and behavior and one more brief computer task about your tobacco purchasing preferences.
• We will provide all the research cigarettes at no cost to you.
• If you take your sessions remotely, we will also give you a mouthpiece you can use to provide the breath samples of recent smoking (exhaled Carbon Monoxide), as well as a machine to measure your puff behavior. The mouthpiece can connect directly to the study smartphone and works with an app.
• If any instructions are not followed, or if your breath sample shows that you have been smoking recently, the session will be cancelled and rescheduled for another time. If you reschedule your visit more than 3 times for any reason, you may be withdrawn from the study.

For a complete description of the study procedures, refer to the Detailed Information section of the consent form.

WHY MIGHT I WANT TO PARTICIPATE IN THIS STUDY?
If you agree to take part in this study, you may benefit directly through increased understanding of factors underlying your use of cigarettes. We also hope that the information learned from this study will benefit other people in the future.
WHY MIGHT I NOT WANT TO PARTICIPATE IN THIS STUDY?

This study has minimal risk however there are known complications that arise from smoking cigarettes that may affect the individual or an embryo, fetus, or infant. The researchers do not know all of the side effects that could happen. For a complete description of known risks, refer to the Detailed Information section of the consent form.

WHAT OTHER OPTIONS ARE THERE?

You may choose not to participate in this study. If at any point during the in-person study visits you decide to stop smoking, you will be reimbursed for your time up to that point and will be able to complete the remainder of the study assessments. We will not ask you to smoke cigarettes if you decide you want to stop smoking. You may choose to decline using the study cigarettes and still be retained in the study and complete all study assessments. We will also provide you with a list of places where you may choose to seek treatment to stop smoking. If you decide to stop smoking at any point you will still be able to continue in the study unless you tell us you want to drop-out of the study.

HOW WILL PARTICIPATING IN THE STUDY AFFECT ME FINANCIALLY?

You will be paid for your time and effort. Below describes the compensation for attending each visit.

Below is a table outlining the schedule of what you might get paid.

In addition to attending 5 sessions in the laboratory, and completing brief surveys about your smoking on a phone, you can be eligible to receive an incentive for returning unused research cigarettes ($0.25 per cigarette), for up to $20 per participant. For returning used cigarettes (e.g., cigarette butts) at Visits 3 and 4 of the study, you will be compensated as follows: $7 for 75-100% returned; $5 for 50%-74% returned, $2.50 for 25%-49% returned; and $0.00 for 0-24% returned.

The total possible compensation (including a one-time referral) is $551. Full payment for the 30-day follow-up and completion bonus will be provided if you complete those portions of the study and when you return the study provided phone and smoking behavior machine (if you use one). You can choose to be reimbursed through Amazon Gift Card code, which is emailed, or a reimbursable gift card which can be given to you directly either via mail or at your first in-person visit. If your first study visit is taken remotely, we can only provide Amazon gift card code as the payment for this session. You may choose reloadable gift card after that session, if you are eligible to continue in the study.

Reimbursable gift cards are provided through Greenphire who is a company working with the researchers and the university. In order to set up and process payments your first and last name, home address, and birth date will be required. When a visit or task is completed, funds will be approved and loaded onto your card. Greenphire will not have access to your research data, only the information required to set up the card.

Note: If during the study your ClinCard is lost or stolen, we will replace it one time, at no charge to you. The new card will be linked to your existing account and the old card will be deactivated. If you lose your ClinCard after your one free replacement you may contact Greenphire, the card issuer, for a replacement for a $7 fee at your expense.

You will be asked to provide you social security number, your residency status (a copy of your green card must be provided if applicable), and whether you are a University of Oklahoma employee for tax reporting.
purposes. If you are unwilling or unable to provide your social security number, residency status (and green card if applicable), or University of Oklahoma employment status you will not be eligible to participate in the research study.

For additional information about possible costs, please refer to the Detailed Information section of the consent form and ask the study team about any expected additional costs or insurance problems.

DETAILED INFORMATION ABOUT THE RESEARCH STUDY

The following pages of the consent form will provide you with more information about this study. Please take your time in reviewing this information and ask the investigator and study team any questions you may have.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 172 people will take part in this study. All of these individuals will participate at this location.

WHAT IS THE STATUS OF THE DRUGS/DEVICES/PROCEDURES USED IN THIS STUDY?

You will smoke your own or usual cigarette brand and very low nicotine research cigarettes in this study. We are calling these research cigarettes. The U.S. Food and Drug Administration regulates cigarettes and the use of very low nicotine research cigarettes (0.4 mg nicotine/g tobacco) in this study is investigational. The word “investigational” means that these cigarettes are not approved for marketing or use as a treatment by the U.S. Food and Drug Administration (FDA). The FDA has allowed research studies in which a person have volunteered to use these cigarettes for testing purposes. The FDA is aware that these cigarettes will be used in this research study. These cigarettes are provided by the National Institute on Drug Abuse Drug Supply Program.

WHAT IS INVOLVED IN THE STUDY?

If you are eligible, this study will require 1 pre-screen/baseline assessment to determine your eligibility, and 5 in-person (or remote) visits to our lab: The baseline assessment will last about 1 hour. If you are eligible and agree to participate, your next 4 visits will be scheduled and will last between 1 and 2 hours, depending on the session. We will ask that you refrain from cigarette smoking and using other nicotine products for at least 12 hours before each experimental visit (in person or remote). You will also be asked not use caffeine (soda, energy drinks, or coffee) for an hour before each experimental session. You will be asked to smoke your usual brand cigarette, and two different types of research cigarettes, each in your home environment for 7 days and then in the laboratory (or remotely). When you are using the research cigarettes for each 7-day period, we ask you that refrain from smoking your usual brand cigarette, and use the research cigarettes instead. One of these research cigarettes will be flavored to taste like mint/menthol and the other will taste like traditional tobacco. These will be very low nicotine research cigarettes that are available from the National Institute on Drug Abuse Drug Supply Program (DSP). The order in which you are assigned to smoke the two types of study cigarettes will be randomly chosen.

If you are female, we will ask you to take a pregnancy test at each experimental study visit. We expect that if you are a female of child bearing age who is able to conceive, you will use reliable contraception and not be planning pregnancy or breastfeeding during the study. Participants with a positive pregnancy test will be notified and will not be able to continue participation in study. If you become pregnant, please let staff know as soon as possible.
Visit 1 (Pre-screen/baseline): We will review eligibility criteria similar to what you answered over the phone. If you are eligible and you agree to participate, we will ask you to provide some additional information about yourself and your use of cigarettes, other tobacco products, and behaviors related to tobacco use.

In Between Visit 1 and Visit 2 (Take Home Smoking): Following Visit 1, you will smoke your usual brand of cigarettes for 7 days, as you normally would. During this 7-day period, you will record your cigarette smoking, mood, and attitudes about smoking twice a day with a smartphone app.

Visit 2 (Smoking Usual Brand Cigarette): You will smoke one of your own cigarettes that you have with you. Before you smoke, we will test your breath to see when you last smoked, and check your heart rate and blood pressure, called your vitals. **For females: We will confirm you are not pregnant with a pregnancy test prior to beginning the session. You will smoke your cigarette through a mouthpiece that allows us to measure the puffs you take. After you finish smoking, we will conduct another breath test, and check your vitals (heart rate and blood pressure). Both before and after smoking we will have you answer some questionnaires about how you are feeling. *If you are taking your visits remotely, we may not be able to take your blood pressure.

At the end of this visit, we will dispense your first set of research cigarettes. We will give you enough research cigarettes to last you for 7-days. This amount will be based on how many cigarettes you typically smoke of your usual brand during a 7-day period. You are not allowed to share research cigarettes or keep them beyond the 7-day period. **If your session is remote, we will arrange a time and day for you to pick-up the research cigarettes, either at our research lab or at a public location (mall, restaurant, library, etc).

In Between Visits 2 and 3 (Take Home Smoking): After Visit 2, you will smoke the first set of research cigarettes in your home environment, for 7-days, and will record your cigarette smoking, mood, and attitudes about smoking and other tobacco use with a smartphone app. We ask that you not smoke your usual brand of cigarettes during this 7-day period. We will ask you to keep track of your used and unused cigarettes, as you return these cigarettes at your next study visit so we can review how many you did and did not use. You are not allowed to share research cigarettes or keep them.

Visit 3 (Smoking Research Cigarette): After using the first research cigarette in your home environment for 7 days, you will return to the laboratory on the 7th day, and smoke that research cigarette, as you wish, through a machine. This smoking session will be identical to the first smoking session. **This visit may occur remotely, if you are unable to return to the lab due to COVID-19. We will also ask you to return used (e.g., butts) and unused research cigarettes. If your session is remote, we will count your used and unused cigarettes during the remote session and then have you return them at your next curbside pick-up/drop-off. You will be compensated for returning used and unused research cigarettes so that we can be sure you have not shared them with anyone.

In Between Visits 3 and 4 (Return to smoking as usual): After Visit 3, you may return to smoking your usual brand of cigarettes, as normal, for 7-days. You do not need to do anything different than you normally would during this week. This is called a "wash-out" period. At the end of the 7-day "wash out" period, you will pick up your second set of research cigarettes. **You will return your used and unused cigarettes at this time and be compensated for used/unused cigarettes. This will take 10-15 minutes. You will then smoke the second set of research cigarettes in your home environment, for 7 days, and will record your cigarette smoking, mood, and attitudes about smoking twice a day with your phone. We will give you enough research cigarettes to last you for 7-days. You are not allowed to share research cigarettes or keep them beyond the 7-day period.
Visit 4: Visit 4 will be identical to Visit 3. After 7-days of using the second type of research cigarette in your home environment, you will return to the laboratory on the 7th day, and smoke that second research cigarette, as you wish, through a machine. We will also ask you to return unused research cigarettes, as well as used research cigarettes (e.g., cigarette butts). If your session is remote, we will count your used and unused cigarettes during the remote session and then have you return them at your next curbside pick-up/drop-off. You will be compensated for returning used and unused cigarettes so that we can make sure you have not shared them with anyone else.

Visit 5: For your final visit, you will be asked to complete a computer task in which can use money to hypothetically pay for and use different amounts of research cigarettes or other tobacco products, or no products at all. This visit will take about an hour. The tobacco products you can buy will be those that are currently available at a local store, as well as the research cigarettes you used over the course of the study. The amount of money that you will have to spend on these products will be based on the typical amount of money you spend on tobacco products each week.

30-Day Follow-up Assessment: Finally, 30-days after Visit 5, we will do a short survey with you, preferably in our lab, but if you cannot make it, we can do it remotely. This survey will ask about your smoking and tobacco use and tobacco-related behaviors. You will also be asked to complete another brief computer task in which can use money to hypothetically pay for and use different amounts of research cigarettes or other tobacco products, or no products at all.

CAN I WITHDRAW FROM THE STUDY?

You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to let the research team know. Refusal to participate or withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you withdraw, you will be compensated for your time up to that point. Your data up to that point may be used for study purposes unless you request otherwise. You can also stop using the research cigarettes at any time without penalty. If you do not want to use the research cigarettes, you may still be able to remain in the study and complete the rest of the study assessments. If you decide you no longer wish to receive the study cigarettes, please let us know as soon as possible.

There may be circumstances under which your participation may be terminated by the investigator without your consent. These include:

- If we believe being in the study may put you at significant risk or feel that it is in your medical best interest
- If you are unable or unwilling to follow study procedures, such as keeping your visit appointments or unwilling or unable to abstain from nicotine or tobacco products and any other combustible product (e.g., marijuana)
- If you are pregnant or breastfeeding, or become pregnant
- The study is stopped by the Sponsor

WHAT ARE THE RISKS OF THE STUDY?

Discomfort from withdrawal: You may experience nicotine withdrawal symptoms during this study. These symptoms can include anger, irritability, frustration, anxiousness, depressed mood, craving for a cigarette, difficulty concentrating, increased appetite, weight gain, sleep problems, restlessness, impatience, constipation, dizziness, coughing, nightmares, nausea and sore throat. These feelings can be uncomfortable, but they are normal, temporary, and are usually mild.
Risks related to smoking: The cigarettes you smoke during this study will be your own brand and the research cigarettes that we provide to you. The research cigarettes contain tobacco and nicotine. All cigarettes, including the research cigarettes, are bad for a person’s health and can lead to heart disease, lung diseases, cancer, and death. Acute side effects of nicotine include headache, nausea/vomiting, increased heart rate, increased blood pressure, runny/stuffy nose, change in taste, heartburn, hiccups, sweating, or diarrhea. Although smoking is associated with disease, we do not expect the disease risk to be significantly greater or lower when smoking the research cigarettes versus the cigarettes you typically smoke. At the end of the study, or if you request, you will be offered resources to help you stop smoking. Quitting smoking can greatly reduce risks to your health.

Discomfort from interview procedures: Some questions may make you feel uncomfortable. You may refuse to answer any questions. However, if you refuse to answer questions that are required to determine your eligibility for the study, you will not be able to continue in the study. There is a potential risk for an unanticipated breach of confidentiality. Below we describe the methods we will follow to ensure your confidentiality is maintained.

The procedures may involve risks that are currently unforeseeable. For more information about risks and side effects, contact the PI Amy Cohn, PhD or the study coordinator Michael Smith at (405) 271-7759, 24 hours a day. We are available Monday through Friday during regular business hours (9-5pm) to return phone calls.

REPRODUCTIVE RISKS FOR WOMEN:
If you are a female, you must not be and should not become pregnant nor breast-feed an infant while this study. Smoking cigarettes while you are pregnant or breastfeeding may involve risks to an embryo, fetus, or infant, including birth defects which are currently unforeseeable. In order to reduce your risk of pregnancy, you or your partner should use one or more of the acceptable methods of birth control listed below, regularly and consistently, while you are in this study.

Acceptable methods of birth control (continuing throughout the study) include:
   - An approved oral contraceptive (birth control pill)
   - Intra-uterine device (IUD)
   - Hormone implants
   - Contraceptive injection (Depo-Provera)
   - Barrier methods (diaphragm with spermicidal gel or condoms)
   - Transdermal contraceptives (birth control patch)
   - Vaginal contraception ring (birth control ring)
   - Sterilization (tubal ligation, hysterectomy or vasectomy)

Certain drugs may interact with contraceptive agents and reduce their effectiveness; therefore, you should inform the study staff of all medications (prescription and over-the-counter) that you are currently taking or begin taking during the study.

IN CASE OF PREGNANCY:
If you become pregnant or suspect that you are pregnant, you should immediately inform the study personnel. We will perform a pregnancy test at each in-person visit or remote study session. If pregnancy is confirmed, you will be withdrawn from the study. Payment for all aspects of obstetrical, child, or related care will be your responsibility. The study doctor and the Sponsor will follow the progress of your pregnancy and will request access to your and/or your infant’s medical records for least eight
TO WHAT EXTENT WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations outside the OUHSC that may inspect and/or copy your research records for quality assurance and data analysis. These organizations may include the US Food & Drug Administration and other regulatory agencies, and the National Institutes of Health. 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 your research records for these purposes.

We work with an internal vendor at our university who supplies the mobile application for the automated daily cell phone surveys. The company will take appropriate steps to protect your privacy. Your information is stored securely and separately from your survey responses. Your personal information will not be sold or given to any other people or companies for any purpose. We also work with an internal vendor (Greenphire ClinCard) who supplies the gift cards you may choose for compensation. This company will not have access to your research data. We do provide this company your name, address, and birth date in order to set up the automatic study payments.

Posting Study on ClinicalTrials.gov:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. However, this website will not include information that can identify you. At most, the website will include a summary of the study and results. You can search this website at any time.

Certificate of Confidentiality:
To help protect your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. This Certificate means that the researchers cannot be forced (for example by court subpoena) to share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the U.S. government that is used for checking or evaluating federally-funded projects or for information that must be disclosed in order to meet the requirements of the US Food and Drug Administration.

The protection offered by the Certificate of Confidentiality does not prevent us from being required by applicable state law to report information about suspected or known sexual, physical, or other abuse of a child or older person, or a subject’s threats of violence to self or others. If any member of the research team is given such information, he or she will be required to make a report to the appropriate authorities. The Certificate, however, does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information. This means that you and your family should actively protect your own privacy.
Identifiable Private Information:
- Your information may be used for future studies without your additional consent. We will remove direct identifiers from your information/specimen 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 your information is shared with another investigator for research purposes, they will not be able to re-identify you.

WHAT ARE THE COSTS?
You may have some travel costs for your study visits and you will be using your own cigarettes for part of the study. If you use your personal phone to complete the daily automated phone calls, we will reimburse you $40 for the month that you have it, or you may have a study phone provided to you if your phone does not have the Android operating system. There are no other costs to you.

WHAT IF I AM INJURED OR BECOME ILL WHILE PARTICIPATING IN THIS STUDY?
You will be watched throughout the study for Adverse Events. All Adverse Events will be recorded and will be followed until they are resolved or stabilized. Formal policies are in place for emergency procedures. In the case of injury or illness results from this study, emergency medical treatment is available. Any expenses will be your responsibility. You or your insurance may be charged for this treatment. Complications arising as a result of the natural progression of an underlying or pre-existing condition will be billed to you or your insurance. Please check with the investigator or with your insurance company if you have questions.

No other funds have been set aside by the University of Oklahoma Health Sciences Center, to compensate you in the event of injury, illness, or for other damages related to your event of injury or illness.

WHAT ARE MY RIGHTS AS A PARTICIPANT?
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare, or willingness to continue your participation in this study.

You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished. You consent to this temporary restriction.

DO I HAVE ANY OTHER RIGHTS OVER MY DATA?
Depending on where the sponsor for your study is located and other factors, you may have additional rights over your personal data collected in this study. For example, the European Union General Data Protection Regulation (GDPR) and some state privacy laws might apply. If the GDPR applies, generally you may have the following rights:

1. The right to request the information collected to be corrected.
2. The right to withdraw your consent for the use of your personal information at any time.
3. The right, in some circumstances, to receive your personal information in a structured, commonly used and machine-readable format and the right to provide your information to a third party.

4. The right to strict confidentiality of your personal data when it is used/shared.

5. The right to limit the use/sharing of your personal information in certain circumstances.

6. The right under some circumstances to request the erasure of your personal data.

7. The right to file a complaint with a privacy protection regulator if you believe any of the rights above have been violated.

You can receive more information regarding these rights in the Privacy Notice for Research Participants, located on the OUHSC Office of Human Research Participant Protection (HRPP) website at [https://compliance.ouhsc.edu/HRPP/Participant/Privacy-Notice](https://compliance.ouhsc.edu/HRPP/Participant/Privacy-Notice).

If you have any questions and requests, please contact the HRPP Office at 405-271-2045.

**WHOM DO I CALL IF I HAVE QUESTIONS, SUGGESTIONS, OR CONCERNS?**

If you have questions, concerns, or complaints about the study or have a research-related injury, contact Amy M. Cohn, PhD or the study coordinator Michael Smith at 405-271-7759 or at Enhance@ouhsc.edu.

If you cannot reach the Investigator or wish to speak to someone other than the investigator and for questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection, at 405-271-2045.

**SIGNATURE:**

By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document.

I agree to participate in this study:

______________________________________ ____________________________      __________

PARTICIPANT SIGNATURE (age ≥18)  Printed Name         Date

______________________________________ ____________________________     ___________

SIGNATURE OF PERSON     Printed Name                    Date

OBTAINING CONSENT