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Impact of a Reduced Nicotine Standard on Young Adult Appeal for Menthol and Non-Menthol Cigarettes

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

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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 (VLNC) 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.

Trial registration number NCT04340947.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is the first study to examine differences in subjective response to menthol and non-menthol very low nicotine cigarettes (VLNCs) specifically in young adults, using laboratory assessments, behavioural economic paradigms and daily diary surveys.
- ⇒ Laboratory studies have high internal control, allowing for causal inference of acute subjective response to menthol smoking, and daily diary surveys allow for measurement of context-dependent fluctuations in cigarette smoking appeal in the natural environment.
- ⇒ Experimental Tobacco Marketplace paradigms allow for the assessment of shifts in tobacco use behaviours in response to different hypothetical policy scenarios.
- ⇒ This project will inform Food and Drug Administration policies by providing evidence of intended and unintended consequences of a reduced nicotine standard in the absence or presence of a menthol cigarette ban.
- ⇒ Only menthol cigarette smokers are enrolled.
- ⇒ This study does not examine how non-menthol cigarette smokers respond to low nicotine cigarettes.

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.^{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 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.^{10 12 18} The study will measure reinforcement for smoking experimental (SPECTRUM variable nicotine research cigarettes) menthol and non-menthol VLNCs (0.03mg) and the impact of proposed product standards and policy scenarios on tobacco product purchasing behaviour using a validated Experimental Tobacco Marketplace (ETM).^{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 ≤ 6 ppm 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 $\geq 80\%$ of the time)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 breast feeding (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)

Table 1 Schedule of enrolment, study visits and assessments

Timepoint	Study period										
	Screening	Laboratory visits/Daily monitoring									Follow-up
	0	Visit 1	EMA	Visit 2	EMA	Visit 3	Washout	EMA	Visit 4	Visit 5	30 Days
Enrolment:		X					–				
Eligibility screen	X						–				
Informed consent		X					–				
Pregnancy urine test		X		X		X	–		X		
Interventions:							–				
Random number generation				X		X	–		X	X	
Smoke usual brand cigarette			X	X			–				
Smoke VLNC 1					X	X	–				
Smoke VLNC 2							–	X	X		
Assessments:							–				
Tobacco use behaviour	X	X	X	X	X		–	X		X	X
Subjective response to smoking		X	X	X	X	X	–	X	X		
Cigarette smoking frequency		X	X	X	X		–	X			X
Smoking topography (eg, puffing behaviour)		X		X		X	–		X		
Experimental Tobacco Marketplace							–			X	X

EMA=ecological momentary assessment daily monitoring.
EMA, ecological momentary assessment.

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 their last study visit (either in person or remotely) 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 *Adverse Events Questionnaire* asks about adverse events experienced since the last visit.

Past 7-day tobacco use will be measured in two different ways. First, at 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 CPT^{38 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 *MNWS*⁴¹ 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*.⁴⁸ 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 precigarette and postcigarette 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 \leq 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*^{35 36} for their usual brand of cigarettes and the *ATSQ*²⁸ 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*^{43 45} in addition to the *N-DEQ*⁴⁷ the *DSQ*⁴⁶ and the *MNWS*^{49 50} 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 postsmoking 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 ≤ 6 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*,³⁷ 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) to be dispensed the first set of VLNC study cigarettes. During the 7-day washout period between visit 3 and visit 4, participants (remote and in-person) will return to the study site or will meet a team member in the community to be dispensed the second set of study cigarettes to smoke 'at home' for the 7 days prior to visit 4. Prior to distributing the second set of VLNC study cigarettes, participants will complete an adverse event form and health changes questionnaire during the VLNC pick-up appointment.

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 $\times 125\% \times 7$ 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% returned, 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\$30) 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.

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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.

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