Study Title for Participants: "Perceptions of Smoking cigarettes in young adults (PRISM)"

Grant title: Measuring young adult appeal for menthol cigarettes using laboratory and intensive longitudinal methods

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Abstract

Although the FDA banned characterizing flavors in cigarettes, menthol cigarettes are still available to consumers. Menthol cigarette smoking has increased in young adults (YA; defined here as ages 18-26), while non-menthol smoking has decreased in this age group, and the majority of new YA smokers initiate with a menthol cigarette. [1,2] Experimentation with menthol cigarettes, vs non-menthol cigarettes is linked to greater likelihood of progressing to regular smoking and nicotine dependence. Menthol's pleasurable taste and other sensory effects (cooling /soothing sensations in the throat) may contribute to a positive first smoking experience,[3] a potential mechanism linking initiation with uptake and regular smoking. A key unanswered question is whether menthol increases the appeal and reinforcing properties of cigarette smoking beyond non-menthol smoking[3,18], which may facilitate progression to regular smoking among newer users. The subjective appeal and reinforcing effects of smoking are important indicators of the neurobiological systems that underlie smoking addiction and abuse liability, and have been shown to

motivate subsequent smoking.[4,5] Only a handful of controlled investigations have examined the differential rewarding/reinforcing effects of smoking menthol and non-menthol cigarettes, but most have methodological limitations, including small sample sizes and omission of YA smokers. These studies also do not measure, with a sufficient level of accuracy, degree of sequencing, and timing that is needed to address the context-dependent fluctuations in menthol-related appeal and reinforcement in real time.

We will recruit menthol (n = 125) and non-menthol (n = 125) YA smokers who initiated smoking in the past 12months or initiated regular smoking more than 12 months ago, and measure appeal/reinforcement for menthol and non-menthol cigarettes and the impact of appeal/reinforcement on changes in smoking (progression, nicotine dependence, and cigarette harm perceptions) at a 6-month follow-up. Appeal/reinforcement will be assessed via two complementary measurement paradigms: one in the laboratory using a well-validated behavioral economic choice task and the other in the natural environment using ecological momentary assessment (EMA). Laboratory studies provide a great deal of efficiency and internal control, allowing for causal inference of acute subjective response; while EMA allows for similar causal sequencing of behavior, but in an ecologically valid format in the smoker's natural environment. It is hypothesized that, compared to non-menthol smokers, menthol smokers will show greater appeal/reinforcement, both in the laboratory and via EMA, and will be more likely to show progression to regular smoking, increases in nicotine dependence, and lower cigarette harm perceptions by a 6-month follow-up. The association between menthol preference and smoking outcomes will be reduced or non-significant after including measures of appeal/reinforcement in the model; suggesting that menthol's appeal/reinforcement accounts for smoking progression. This research will isolate the unique effects of menthol in smoking and will help inform regulatory decisions about the abuse liability of menthol cigarettes and the use of flavors in other tobacco products in future studies.

Background and Significance

Although the FDA banned characterizing flavors in cigarettes, menthol cigarettes are still available to consumers. Menthol cigarette smoking has increased in young adults (YA; defined here as ages 18-26), while non-menthol smoking has decreased in this age group, and the majority of new YA smokers initiate with a menthol cigarette Experimentation with menthol cigarettes, vs non-menthol cigarettes is linked to greater likelihood of progressing to regular smoking and nicotine dependence. Menthol's pleasurable taste and other sensory effects (cooling /soothing sensations in the throat) may contribute to a positive first smoking experience, a potential mechanism linking initiation with uptake and regular smoking. A key unanswered question is whether menthol increases the appeal and reinforcing properties of cigarette smoking beyond non-menthol smoking[3,18], which may facilitate progression to regular smoking among newer users. The subjective appeal and reinforcing effects of smoking are important indicators of the neurobiological systems that underlie smoking addiction and abuse liability, and have been shown to motivate subsequent smoking. Only a handful of controlled investigations have examined the differential rewarding/reinforcing effects of smoking menthol and non-menthol cigarettes but most have methodological limitations, including small sample sizes and omission of YA smokers. These studies also do not measure, with a sufficient level of accuracy, degree of sequencing, and timing that is needed to address the context-dependent fluctuations in menthol-related appeal and reward in real time.

Study Objective

We will enroll menthol (n = 125) and non-menthol (n = 125) YA smokers who initiated regular smoking in the past 12-months or who initiated regular smoking more than 12 months ago, and measure appeal/reinforcement for menthol and non-menthol cigarettes and the impact of appeal/reinforcement on changes in smoking (progression, nicotine dependence, and cigarette harm perceptions) at a 6-month follow-up. Appeal/reinforcement will be assessed via two complementary measurement paradigms: one in the laboratory using a well-validated behavioral economic choice task and the other in the natural environment using ecological momentary assessment (EMA). Laboratory studies provide a great deal of efficiency and internal control, allowing for causal inference of acute subjective response; while EMA allows for similar causal sequencing of behavior, but in an ecologically valid format in the smoker's natural environment. It is hypothesized that, compared to nonmenthol smokers, menthol smokers will show greater appeal/reinforcement, both in the laboratory and via EMA, and will be more likely to show progression to regular smoking, increases in nicotine dependence, and lower cigarette harm perceptions by a 6-month follow-up. The association between menthol preference and smoking outcomes will be reduced or non-significant after including measures of appeal/reinforcement in the model; suggesting that menthol's appeal/reinforcement accounts for smoking progression. This research will isolate the unique effects of menthol in smoking and will help inform regulatory decisions about the abuse liability of menthol cigarettes and the use of flavors in other tobacco products in future studies.

Specific Aims

Aim 1 (Phase 1): Examine the absolute and relative reinforcing value (appeal) of menthol vs. non-menthol cigarettes using a validated laboratory-based behavioral economic choice task.

Aim 2 (Phase 2): Examine the subjective effects (appeal) of menthol vs. non-menthol cigarettes (own brand) during 14 days of ecological momentary assessment (EMA) in the natural environment.

Aim 3 (Phase 3): Examine the degree to which laboratory (Phase 1) and EMA (Phase 2) measurements of menthol appeal/appeal causally impact (i.e., mediate) the association between menthol brand preference at baseline and 6-month smoking outcomes (progression, increased nicotine dependence, lower cigarette harm perceptions).

Study Design

This is a 3-phase study. The first phase will occur in the Health Promotion Research Center in Oklahoma City, OK and will include 3 in-person study visits. The second phase will occur via twice daily brief cellphone based survey assessments that will automatically be deployed on the participant's cell phone (or a study provided phone) via a mobile application. The third phase of the study consists of an approximately 6-month follow-up after baseline to determine changes in smoking behavior. Brief interim surveys at 2 and 4-months post-enrollment will be added to enhance retention rates. The follow-ups can occur in person, over the phone, or online, to reduce participant burden.

New methods addressing COVID-19 restrictions when in-person study visits are not allowed or cannot be conducted.

The order in which study phases occur may differ in response to the COVID-19 virus. When the university is operating "as normal", participants will complete the 3 in-person laboratory sessions first (Phase 1), and then complete the daily phone assessments immediately after the final in-person session (Phase 2), and then the final follow-up survey (Phase 3). They will complete the baseline survey during the first in-person visit.

If a participant is recruited and enrolled when in-person data collection activities are limited or restricted due to COVID-19, online consent and online baseline survey will be offered in order to address current restrictions on in-person data collection. They will be asked to provide consent online (by electronically signing the consent document), complete the baseline survey online, and then begin the daily phone surveys immediately after that (Phase 2). See below for consenting process online. If the person would like to complete the smoking sessions in person, once in-person data collection can begin (Phase 1), a member of the research team will contact participants to determine if they are still interested in participating in Phase 1 in-person sessions, and determine if they are eligible to participate (e.g., still smoking, not currently pregnant/breastfeeding/planning to become pregnant). If they are interested and meet eligibility criteria, they will be scheduled for the 3 in-person laboratory sessions. We will make every effort to contact participants and schedule those sessions as soon as possible after they enrolled. Given the uncertainty of the COVID-19 outbreak, we cannot determine how long participants may need to wait. Additionally, remote smoking sessions will be offered to ensure data collection for individuals that are not comfortable with in-person visits or in the event they are unable to enter the laboratory setting. During the screener, participants will be asked if they would like to attend socially distanced in-person visits, or remote study sessions.

Study Products

Study Cigarettes. Using procedures similar to Strasser and colleagues commercially available Camel Crush cigarettes (R.J. Reynolds, Winston-Salem) will be used for both menthol and non-menthol smoking in Visit 2. [6] We chose these because they contain a small, menthol-filled capsule that breaks open when squeezed and releases menthol into the cigarette. They are well suited to isolate menthol's effects because there is no menthol flavor prior to squeezing, minimal menthol variation after crushing, and similar levels of nicotine, cotinine, and NNK, before and after crushing They are also ideal because they are not popular among our typical participants (i.e., < 1 in 125 participants), based on analysis of PATH Wave 1 data, and have nicotine levels comparable to the very popular brands of Newport (0.8 mg) and Marlboro (0.8 mg). Thus, Camel Crush cigarettes will allow us to isolate menthol's effects in the absence of cigarette loyalty or familiarity, and the other potential differences between cigarette types other than menthol level.

Study Procedures

Phase 1 Overview and Experimental Design

Phase 1 (Aim 1) will take place in the laboratory at Health Promotion Research Center (HPRC), in Oklahoma City, OK. A 2 (menthol preference: yes/no) X 2 (cigarette type: usual brand versus experimental cigarette) factorial design will be used with cigarette type as a within-subjects factor. After determining initial eligibility via telephone and/or online, ≥ 12-hour abstinent smokers (CO-verified ≤8 ppm) will attend each of 3 lab visits scheduled around the same time of day and separated by at least 48 hours (from start time

to start time). The participant will attend an initial baseline visit, where informed consent will be completed and a baseline experimental visit of ad libitum smoking of one's preferred cigarette brand, and two additional visits later. The ≥ 12-hour abstinence requirement was chosen because it controls for recent smoking exposure and produces optimal levels of smoking motivation that are sensitive to the experimental manipulations[7] including the paradigm used in the current proposal, and prevents greater attrition and non-compliance relative to more prolonged periods.[157] Participants will be compensated $45 for each in-person laboratory smoking visit in which they are eligible, or $25 for Visit 1 if they are deemed ineligible. Participants will also be compensated $35 for completing the baseline survey. Individuals will be compensated $10 for each in-person visit (up to $30).

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

PROCEDURE:

1. Employees will comply with all OUHSC COVID related policies and procedures as currently exist and as are revised in the future.
2. Efforts will be made to minimize face-to-face time with participants. When possible, consents will be sent to participants at their homes and reviewed by phone or zoom, as available. Additional items, including pregnancy tests, will also be shipped to the home, and reviewed over phone or zoom, when possible.
3. During scheduling, participants will be asked to wear a mask, if they have one available, to their appointments. For participants who do not have access to a face mask, they will be told that one will be provided. They will also be asked the questions from the OUM/OUHSC COVID19 Questionnaire (see attached in "Other Documents"). If the patient is symptomatic or has known direct contact with a person with COVID-19 they will be asked to consult with their PCP prior to re-scheduling their visit.
4. Participants will be instructed to call from their vehicle upon arrival for their appointment to prevent participants from congregating in the waiting room. They will also be verbally asked if any of their answers from the COVID-19 questionnaire have changed since their original completion. If the patient is symptomatic or has known direct contact with a person with COVID-19 they will be asked to reschedule their appointment.
5. If a room is not available, the participant will wait in their car and the study coordinator will call them once space is available. We will make every effort to ensure that the assigned research room will be available by spacing apart study sessions.
6. Participants will have their temperature taken using a contactless thermometer prior to entering the facility. If the temperature is above at or above 100.0°F they will not be seen and will be advised to contact their PCP for further assistance.
7. Participants will not be allowed to have a second individual accompanying them or waiting in the waiting room unless previously approved for special circumstances by study staff.
8. Upon entering research rooms, proper hand hygiene will be executed by study staff and participants. Study staff will be gloved for any touch-related interactions with the participant. Hand sanitizer will be available for participant use as well.
9. Staff will wear proper PPE at all times.

10. To reduce viral transmission, study staff will be seated in a separate room from the research participant during the visit. Communication with the participant will occur by video and audio connection between the staff "control room" and the participant's research room. All participants will be placed in a negative pressure room that is specifically designed to circulate the air outside of the room every 10 minutes; thus reducing exposure to viral droplets.
11. To reduce viral transmission during and between shifts and following interaction with participants, all spaces will have available cleaning products containing 70% ethanol to disinfect surfaces, door knobs, and equipment surfaces frequently, between each research participant, and at the beginning and end of a shift and before and after each participant. Common equipment in shared areas will be disinfected with 70% ethanol prior to and after each use.

Remote Data Collection Procedures due to COVID-19

Participant recruitment will remain the same, as described above in the recruitment section. As originally outlined, recruitment documents will direct potential participants to call the study phone number to complete the initial screening by phone, or a web-link to complete the initial screening online. Study personnel will call all potentially eligible individuals who were screened online to confirm eligibility.

After an initial screen and confirming eligibility, individuals who are interested in participating will be invited to complete the consent form and a baseline survey online. After completing the baseline survey, participants will begin the Phase 2, which is 14-days of daily monitoring of their smoking behavior. Study personnel will schedule a 10-minute phone call with the respondent prior to this, to review and provide a brief training on how to use the daily survey system. At the completion of daily monitoring, participants will complete a brief assessment online to query about satisfaction with and reactivity to the daily surveys. This is the 2-week follow-up survey.

COVID-19 accommodations for measuring smoking behavior and expired carbon monoxide:

The SODIM Smoking Puff Analyzer Mobile SPA-M will be used to allow ambulatory smoking behavior to be recorded remotely from the participant's home. The unit will record time, puff duration, volume of smoke inhaled and pressure drops and calculate averages and standard deviations. By using this device the study will be able to collect smoking topography remotely. The ability to collect this vital data will be important to ensure the study can maintain data collection for specific aims of the study for individuals who are not comfortable or are unable to enter the laboratory setting. Additionally, pregnancy tests will be sent to relevant individuals for exclusion confirmation prior to smoking procedures.

Participants will also be provided a smartphone compatible portable carbon monoxide (CO) monitor (Bedfont iCO Smokerlyzer) and asked to complete iCO reading to verify smoking status at the beginning of each remote (video) smoking session ($\leq$8ppm) and exhaled CO (exposure) following smoking.

Participants will be prompted to connect the iCO device to the study smartphone at the beginning of each study session. They will follow step-by-step instructions to complete the iCO test provided on the smartphone app, and can be assisted by the study staff member during the video call. Results of these tests will be date and time stamped. Each participant will be provided their own iCO Smokerlyzer free of charge. This iCO procedure has been approved for use in several other OUHSC IRB-approved studies.

Participants will be asked and reminded not to send PHI via email or any other unapproved system. Research data will only be collected and recorded via approved data collection systems (e.g. REDCap and mHealth Insight)

Laboratory Visit /Session 1: Baseline Assessment and Ad Libitum Smoking. Visit 1 (between-subjects) will measure absolute reinforcing value (ARV) of menthol vs non-menthol cigarettes via a 60-minute ad-libitum smoking session of one's usual cigarette type (menthol or non-menthol). Subjective response (e.g., smoking satisfaction, craving reduction, psychological reward, sensory effects like throat hit), smoking exposure (CO boost), and behavior (topography: number of puffs, total time smoked) will be measured.

After completing the initial screening over the phone, participants will be informed of the study procedures and invited to the lab to complete the three laboratory visits (If in-person data collection is occurring and if they choose to come to the laboratory). During scheduling for Visit 1/Session 1, they will be reminded to bring at least two of their cigarettes to the first study visit and will be asked to abstain from nicotine and tobacco products, and any other combustible product (e.g., cannabis) for at least 12 hours prior to each study visit. If they are going to attend an in-person session, they will be reminded to wear a mask and that they will be asked about any changes in the COVID-19 screener since they were first asked. If an individual selects virtual study sessions, they will be asked to complete the visit 1 procedures remotely using a remote topography device and iCO carbon monoxide reader to confirm smoking recency. In-person participants will provide a breath sample to measure carbon monoxide levels and asked when the last time they smoked a cigarette was. We will use password protected video conferencing to allow study staff to assist participants and complete this and the below procedures.

After completing questionnaires, ARV will be measured by having participants smoke their usual brand of cigarette (*ad libitum*), which they will be instructed to bring with them to the first study visit. They will smoke through a mouthpiece of the Cress Smoking Topography Device, during a 60-minute smoking Visit or the SODIM Smoking Puff Analyzer Mobile SPA-M The CReSS or SODIM instrument will record puff volume, duration and velocity and inter-puff interval for each puff and their aggregate averages. [7-10]Puff topography measures will be used to examine whether increased puff volume, duration, and lower inter-puff interval differ across menthol and non-menthol cigarettes. Before and after smoking, heart rate and blood pressure will be collected (if session is taken in person); exhaled carbon monoxide (CO boost), and subjective response to smoking (craving reduction, psychological reward, satisfaction, sensory effects) using the Cigarette Evaluation Questionnaire (CEQ). Exhaled carbon monoxide will be collected and measured in ppm immediately before and after smoking. At the completion of Visit 1, participants will be paid for the visit, and scheduled for study visits (V2 and V3).

Laboratory Visit or Session 2: Sampling Experimental Cigarettes and Cross-Price Elasticity Task**.** Participants will confirm abstinence by being asked the last time they smoked a cigarette in addition to providing a carbon monoxide measurement (CO $\leq$ 8 ppm). Visit/Session 2 (within-subjects) will familiarize participants with the experimental cigarette (Camel Crush) by having them take a minimum of 3 and up to 5 puffs each of a menthol and non-menthol version (counterbalanced) and complete subjective ratings,

smoking exposure (CO boost), and behavior (topography: total time smoked). There will be a 20 minute washout period between each cigarette smoked, per our consultant's (Dr. Audrain-McGovern) paradigm protocol[11-14]. Before and after smoking heart rate and blood pressure will be recorded (if session is taken in person), approximately 5 minutes after smoking subjective response, and CO boost will be recorded. After another 20 minute wait period from the last cigarette puff.

After another 20-minute wait period to reduce satiation and increase desire to use, reinforcement of the experimental cigarette brand (matched on flavor preference), participants will be assessed on the reinforcing value (RRV) of the experimental cigarette brand vs their usual cigarette brand (matched on flavor preference) via a behavioral economic purchase task to assess cross-price elasticity. For this task, participants will be asked to report hypothetically how many of the experimental cigarettes they would buy and smoke at increasing prices of their preferred cigarette brand. This task determines how reinforcing the experimental cigarettes (of the same flavor) is to one's usual brand, in order to isolate the effects of menthol flavoring from brand preferences in final outcome analyses. Reinforcement will be defined by the breakpoint, or the highest trial (out of 10 trials) that will be completed for cigarette puffs of the experimental brand choice task. This is a questionnaire and participants will not actually smoke any additional cigarettes after completing this questionnaire. If an individual is unable to come to the lab due to COVID-19, they will be asked to complete the visit 2 procedures remotely using a remote topography device and iCO carbon monoxide reader via password protected video conferencing to allow study staff to assist participants and complete this and the below procedures.

Laboratory Visit 3: Behavioral Economic Choice Task and EMA Training. Visit/Session 3 (within-subjects) will assess the relative reinforcing value (RRV) of menthol vs non-menthol usual brand cigarettes via a computerized behavioral economic choice task that will evaluate participants' willingness to "work" to hit targets on a computer screen to earn puffs of a menthol or non-menthol cigarette. Following confirmation $\geq$ 12-hours of abstinence (expired CO $\leq$ 8ppm) and answering when the last time they smoked was. Participants will complete a behavioral economic choice task in which they can earn points for puffs of a menthol versus non-menthol cigarette of their usual brand. Images on the choice task will be brand neutral and include an image of a cigarette with a mint/menthol leaf and an image cigarette with a brown tobacco leaf to indicate menthol and non-menthol flavoring. With this choice task, we are able to isolate the unique effects of menthol on smoking by controlling for the potential impact of cigarette brand familiarity on ratings of RRV.

Using a concurrent schedule, participants will be able to switch from working on one screen to the other as often as they desire. Consistent with relative reinforcement paradigms, the reinforcement schedule in the non-menthol earning screen will remain constant at a fixed ratio FR-25 (25 targets achieved to earn a point) while the reinforcement schedule for the menthol cigarette will increase (require more effort) with a progressive ratio schedule of PR–25 x over 10 trials, such that 25, 50, 75, 100, 125, 150, 175, 200, 225, and 250 targets have to be "hit" to earn a point.

The choice task determines how reinforcing menthol cigarettes are relative to non-menthol cigarettes (of the same brand) by the participant's willingness to work increasingly harder for puffs of a menthol cigarette vs nonmenthol cigarette. Reinforcement will be defined by the breakpoint, or the highest trial (out of 10 trials) that will be completed for menthol cigarette puffs.

The computer task will be performed until 10 trials are completed and a total of 10 points (or puffs) are accumulated. Per paradigm protocol, cigarette puffs earned are taken at the end of the procedure.[21] Following the choice task, participants will be able to smoke the cigarette puffs they earned (up to 10 puffs). As in Visits 1 and 2, subjective response (e.g., smoking satisfaction, craving reduction, psychological reward, sensory effects like throat hit), smoking exposure (CO boost), and behavior (topography: number of puffs, total time smoked) will be measured.

To ensure that choice task responses are based on reinforcer preference rather than departure from the laboratory, the choice task will be followed by a 30-minute wait in the laboratory (if the session is taken in person). If the session is taken remotely, there may not be a 30-minute wait period. During this 30-minute wait period, participants will be queried about potential reactivity (i.e., behavior change or increased awareness of behavior and attitudes) to the laboratory visits with a brief survey. They will then be given instructions for the EMA phase of the study (Phase 2). During this training, participants will complete a practice survey from their phone. They will be given a wallet sized reference card containing the date range of the monitoring period, the lab study phone number, and a paper copy of the EMA questions and response options.

Table 2. Phase 1 Measures and Schedule of Events Under Normal Operating Procedures

Phase 1 Measures	Laboratory Visit		
	1	2	3
Inclusion/Exclusion			
Informed Consent**	X		
Confirm Abstinence (exhaled CO ≤ 8ppm)	X	X	X
Urine Pregnancy Test	X	X	X
Monitoring for Adverse Events	X	X	X
Pre-Lab Smoking Measures			
Baseline Questionnaire Survey**	X		
Cigarette Purchase Task (part of the baseline questionnaire)**	X		
Behavioral Economic Choice Task			X
Minnesota Nicotine Withdrawal Scale (MNWS)	X	X	X
Questionnaire of Smoking Urges (QSU)	X	X	X
Vital Signs (heart rate (HR) and blood pressure (BP))***	X	X	X
Exhaled carbon monoxide (CO)	X	X	X

Smoking Measures			
Puff Topography	X	X	X
Post-Lab Smoking Measures			
Vital Signs (HR and BP)	X	X	X
Exhaled CO	X	X	X
Nicotine Delivery Effect Questionnaire (N=DEQ)	X	X	X
Duke Sensory Questionnaire	X	X	X
Cigarette Evaluation Questionnaire (CEQ)	X	X	X
MNWS	X	X	X
Other Measures			
Cross Price Elasticity Questionnaires		X	
30-minute wait period			X** (for inperson session)
Monitoring for Adverse Events	X	X	X

** Informed consent, baseline survey, and cigarette purchase task can be completed remotely (e.g., electronically) if participant enrolled during COVID-19 restriction on in-person data collection.

***vital signs will be assessed for in-person sessions.

Phase 2 Overview and Experimental Design

Phase 2 will examine the subjective effects (appeal) of menthol vs. non-menthol cigarettes (own brand) as they occur in the participant's natural environment. To achieve this aim (objective), participants will engage in 14 days of twice-daily ecological momentary assessment (EMA). Following Phase 1 (if recruited during normal operating procedures), participants will complete 14 days of EMA of smoking behavior and subjective response (satisfaction, craving reduction, psychological reward, sensory effects like throat hit) twice a day, smoking as usual. NOTE: If participants are enrolled when there are COVID-19 restrictions on in-person data collection, they will begin the daily EMA after they complete the baseline survey, and before they attend the 3-person visit lab visits. Participants will answer a set of questions about their smoking behavior by responding to a series of survey questions that will be deployed on an app installed on their phone (or a study provided phone if their phone is not compatible with the app. The app is only available only on the Android platform). Phones will be mailed back to the study lab at the end of the 14day monitoring period using a pre-addressed stamped envelope provided by the study team. Prompts (e.g., notifications to the telephone) will be programmed to occur at random times within each of two 4hour time blocks, one corresponding to the morning and one the evening. Prompts will be programmed to coincide with respondents' sleep-wake cycle (i.e., the usual time they wake up and go to bed). Sleep/wake cycle will be collected at the baseline visit. At the completion of EMA, participants will be

asked to participate in a brief assessment to query about satisfaction with and reactivity to the EMA assessments. They will get paid $15 for this survey. EMA entries are expected to last ~5 minutes (based on response times in prior studies). Participants who miss EMA surveys or the EMA reactivity survey will be given the opportunity to complete the surveys by invitation via REDCap.

Phase 3 Overview and Experimental Design

Phase 3 will examine the degree to which laboratory and EMA measurements of menthol appeal causally impact (i.e., mediate) the association between menthol brand preference at baseline to 6-month smoking outcomes. Participants will complete a follow-up survey that will be scheduled to occur 6 months after they are enrolled in the study to assess cigarette smoking (frequency and intensity in the past 30-days), nicotine dependence, absolute smoking harm perceptions ("How harmful are cigarettes to your health?"), and relative smoking harm perceptions ("Compared to non-menthol cigarettes, how harmful to your health are menthol cigarettes?"). Follow-up assessment can be completed either in-person, or via telephone or web-assessment (if in-person follow-up is not viable). Participants will also be asked to complete two interim assessments (2-months and 4-months post enrollment) to enhance retention rates through the 6-month follow-up. These surveys will be brief and query about tobacco use behavior in the past 30-days. Participants will be given a reminder notification approximately two-weeks before their scheduled follow-up assessment (timeframe may be a few days longer or shorter due to holidays). All other baseline variables will be re-assessed at the follow-up, in addition to questions about cessation attempts and new tobacco product initiation, including flavored tobacco use (where applicable). We will use several strategies to encourage completion of the study by providing participants: 1) a calendar of their appointments throughout the study; 2) reminder calls the day prior to a scheduled visit; 3) monetary incentives at each visit; and 4) a completion bonus.

Participants

Participants will be n = 125 menthol and n = 125 non-menthol young adult (YAs) who started smoking regularly in the past 12-months or initiated regular smoking more than 12 months ago.

Participant Recruitment

Participants will be recruited from Oklahoma City, and surrounding metro area (Edmond, Norman) using methods that we have used in previous laboratory studies: local newspapers (including at local colleges/universities), radio, online (e.g., craigslist; Facebook; Instagram,), community flyers, snowball techniques, and our database of interested callers from past smoking studies. These strategies have been successful in studies conducted by the team members at recruiting smokers across the age spectrum for both laboratory and EMA studies. Advertisements will only be placed on US-based sites/portals/webpages and all Facebook/Craigslist/other online ads will be limited to US-based locations. A link to the online study screener will be provided for online postings, so that potential subjects can click and be directly taken to the study screener. For print ads, we can use a QR code, where space is available. The laboratory's close proximity (<10 -20 miles) to several colleges and universities, will further aid in our ability to recruit the sample within the allotted time frame.

In addition to traditional laboratory recruitment with flyers, we will use Trialfacts, who will assist with recruitment by designing and managing targeted, GCP-compliant, IRB approved advertising. Potential

participants who express an interest will click on a Trialfacts-generated ad and will be taken to a custom landing page created by Trialfacts. This landing page will offer a brief description of the study that is designed to convert interest into engagement. After clicking on the ad, participants will review the Trialfacts Consent to continue (attached as part of the Trialfacts pre-screener) and will only be able to provide their contact information and continue with the Trialfacts pre-screener if they select "Yes" in response to "Are you willing to continue." Individuals who select "No" will not continue with the prescreener.

After completing the Trialfacts Consent, individuals will have the ability to fill out an initial Trialfacts screening form online (called pre-screening) and those who pass the Trialfacts online pre-screening questionnaire may select a specific time slot to book an appointment with an OUHSC staff member to confirm eligibility over the phone. Thus, potentially eligible respondents are pre-screened by Trialfacts and only the participants that pass the pre-screen are scheduled with the OUHSC research staff for a phone screen appointment to confirm eligibility. Trialfacts refers potentially eligible individuals to OUHSC team. If they choose not to book an appointment, they will be provided with the necessary information to be able to get in touch with the OUHSC research study staff at their own time. Trialfacts adheres to data security and privacy standards consistent with HIPAA. Pre-screening potential participants and scheduling phone time with research assistants will greatly help with initial engagement in the research Individuals who fail the Trialfacts pre-screening questionnaire are notified by Trialfacts that they are not eligible to participate in the study, and are thanked for completing the pre-screening questionnaire. These individuals are not passed along the OUHSC research team.

We have included the landing page information, recruitment questionnaire, confirmation texts and emails, the list of headline and ad text options for advertisements, as well as wording for the landing page.

In addition to the aforementioned recruitment methods, we will use BuildClinical, who will assist with recruitment by designing and managing targeted, GCP-compliant, IRB approved advertising. BuildClinical is a data-driven software platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. BuildClinical utilizes study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online pre-screen questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer (SSL) software, which encrypts all inputted information, keeps participant information private and HIPAA compliant. BuildClinical's backend servers are stored in the USA at some of the most secure data centers in the world. The study team will access BuildClinical's platform to review and select qualified screening participants for additional screening. Interested individuals may then choose to enroll in the study by completing Informed Consent and HIPPA prior to scheduling a baseline lab or virtual session.

We have included the BuildClinical advertisement materials, pre-screening questionnaire, and study information landing page design and

content.Inclusion/Exclusion criteria

Inclusion criteria:

(1) Ages 18 to 26;

(2) Currently smoke cigarettes “somedays” or “everyday”;

(3) Started smoking "somedays" or "everyday" in the past 12-months or more than 12 months ago.

(4) A strong preference for menthol or non-menthol cigarettes (i.e., smoke one type ≥80% of the time.

(5) Able to read and understand the informed consent

(6) Willingness to abstain from nicotine containing products or other combustible products (e.g., smoked cannabis) for at least 12 hours prior to each in-person or virtual laboratory visit (confirmed by CO ≤ 8ppm for each in-person study visit in Phase 1). Will be rescheduled once if CO is not within acceptable range.

Exclusion criteria:

(1) Current use of nicotine replacement therapy (NRT);

(2) Currently pregnant or planning to become pregnant, or breast feeding (verified by pregnancy test at each study visit/session);

(3) Participant self-reports a diagnosis of lung disease, including asthma, cystic fibrosis, or chronic obstructive pulmonary disease; PI.

(4) History of cardiac event or distress within the past 3-months

Individuals will be provided referrals for treatment at the completion of the study. Men and women of any ethnic or racial group are eligible to participate in the study if they meet inclusion/exclusion criteria.

Update about the impact of Tobacco 21 regulation on study recruitment

Because of the new Tobacco 21 regulations at the state and federal level, individuals under the age of 21 are not allowed to purchase tobacco products, and the research team is no longer allowed to "furnish" tobacco products to individuals under the age of 21 without a research waiver. The Governor of Oklahoma signed SB319 into law on April 22, 2021 which provides an exemption for scientific study from penalties for furnishing tobacco products to persons under the age of 21 years. SB319 is scheduled to take effect on November 1st, 2021. On this date, the research team will begin recruiting persons aged 18-20 years for full participation in the research study.

Informed Consent Process

Participants will provide verbal or electronic consent to be screened over the phone or online, respectively. Verbal consent will be obtained for participants completing the telephone screener. Prior to beginning the telephone screener, participants will be told (a) their research data provided on the telephone screen will be confidential and coded only with a unique identifier; (b) their personally identifiable information will be kept separate from their research data on a password protected server

that can be accessed only by approved study personnel; and (c) there is a possible risk of loss of confidentiality although the risk is considered low given that research data will be de-identified.

If recruited during university normal operating procedures (when in-person data collection is allowed), eligible participants will provide written consent in person immediately before their first laboratory visit begins. This will take place in our lab. We will go over every section of the consent document with the participant, then ask if he or she has any other questions before signing. Each participant will be allowed time to read the consent document and ask questions before any data are collected. A copy of the consent form will be given to the participant.

Electronic Informed Consenting (eIC) process. To provide consent electronically, participants will be sent a link to the eIC via RedCap REDCap has a feature which allows for version control, automatic time and date stamp, and electronic signature (using a fingertip, computer mouse, or stylus on a tablet screen). To ensure that the eIC is presented appropriately and that subjects will have enough time to dedicate to the eIC process, an eligible and interested participant will be told by a study personnel, at the end of the phone screening session, approximately how long the consent review process will take and will review with them the information that will be in the eIC. The eIC will record the timestamp of participant's acceptance or declination and a copy of the signed eIC will be sent to the participant via email. No personal information, other than the participant's name, will be collected in the eIC. Participants will be reminded that their participation is voluntary. Additionally, they will be reminded that they are allowed to discontinue participation in the study at any time, without any loss of benefits or other negative consequences. Participants will be given ample opportunity to read the consent and have any questions related to the consent, the study, or participation answered by the research team member. The participant will have the option to decline participation or withdraw from the study at any time. Individuals will be given as much time as they need to make a decision about participation. If the individual decides to participate, s/he will be given the opportunity to sign the consent and the research team member will sign as a witness (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.

Compensation

All participants will be reimbursed for their participation via cash, gift code, or reloadable gift card. Participants will be compensated using an incentive paradigm to ensure participant retention in all 3 laboratory visits and completion of all daily EMA surveys. Participants will receive $35 for completing the baseline survey, $45 for completing the Visit 1 smoking session, $45 for Visit 2, and $45 for Visit 3. Participants will be compensated upon return of the smartphone after the 2-weeks of EMA monitoring based on the following compensation schedule: They will receive $1 for each completed EMA survey (totaling $28), a $10 bonus each week for completing all EMA surveys in a week period (totaling $20), and a $50 bonus if they complete 85% of the EMA surveys over the courses of two weeks (23/28 surveys). Participants can therefore be eligible to receive a total of $98 if they complete all EMA surveys.

There will be a brief post-EMA survey to assess reactivity, for which they will be paid $15 and then a 6month follow-up for which they will be paid $55. Participants will be compensated $15 each for

completing brief interim surveys at 2 and 4 months post-enrollment. Participants who refer an individual who is eligible and signs informed consent to participate will receive a $25 referral bonus (Limited to one person) and those who complete all phases of the study will be eligible for a $100 bonus. Participants will be compensated $10 for each in person visit if they do in-person sessions. If a participant choses to complete the study remotely, they will be compensated $10 for coming to the research site to pickup/drop-off study materials (e.g., study phone, remote topography machine, experimental Camel Crush cigarettes), up to three times (total of $30 for travel). Total possible compensation will be $523, including the referral bonus. Participants will be asked to provide their social security number, their residency status (permanent residents must provide a copy of their green card if applicable), and whether they are a University of Oklahoma employee for tax reporting purposes. Participants who are not U.S. Citizens or permanent residents or individuals who are unwilling/unable to provide their residency status, social security number, and whether they are a University of Oklahoma employee will be excluded due to the inability to receive study compensation according to the University of Oklahoma Administrative Policy Part 500 Section 557.

Table 1. Compensation Schedule

EVENT	**AMOUNT**
Baseline survey	**$35**
Laboratory Visit	
Visit 1	$45
Visit 2	$45
Visit 3	$45
Bonus for eligible referral (1/person)	$25
EMA	
Call completion (*28 surveys)	$1/call
Bonus for completing all surveys each week (* 2 weeks)	$10
Bonus for completing 85% of all surveys for 2 weeks	$50
Follow-Up	
Post-EMA survey	$15
2 interim assessments (@$15 each)	$30
6-month follow-up	$55
Bonus for completing all phases	$100

Maximum Total	$523
Travel to study site (*3)	$10 per trip ($30 total)

To enhance retention in all phases of the study, we will offer a bonus of remaining incentive amount to participants who are hard-to-reach or schedule. With this bonus, participants will be eligible to receive their maximum amount, if they complete all remaining study sessions and/or surveys. With this approach participants will not be earning more than the maximum amount. It is only to retain people who have not been responsive for study sessions.

Materials

Participants will provide responses to a battery of questionnaires from the PhenX toolkit and those used by the study team, including demographics, tobacco use history and current behavior, tobacco use attitudes and perceptions of harm, and tobacco-related correlates. Smoking urge, subjective response to smoking, and nicotine withdrawal will also be collected.

This study will utilize a mobile phone application provided by the University of Oklahoma Health Sciences Center (OUHSC) MHealth Department to deploy EMA technology. This mobile application has been approved for use by the OUHSC IT. Participants will use their unique identifier number when calling into the system to ensure confidentiality of their automated surveys. Participant responses to study questions will be encrypted and stored on the study smartphone. Encrypted data will be automatically uploaded to a secure server each day. The backend database is hosted by Microsoft Azure and the University of Oklahoma Health Sciences Center (OUHSC) and Azure has been approved by OUHSC risk assessment. The only personnel who have access to the Azure services are the mHealth developers. Study PI's and their designated team members have access to participant data through specified roles with secure logins and can only access data for their own projects. Azure databases are encrypted. Further, the data associated with the mobile app is encrypted. Azure uses TDE (transparent data encryption) AES_256. The database on the app-related phone is encrypted with SQL-Cipher, which also underwent risk assessment and was approved for use by OUHSC. Only research team personnel with specific roles can log in and download data. All study provided phones will be "wiped" and "sanitized" once the monitoring period is complete. The app can be disabled remotely and the phone can be wiped. These steps will ensure the security of EMA data. Software will be downloaded onto each study phone so that phones can be remotely wiped if lost or stolen. A copy of the mHealth privacy statement will be available to each participant during the consent process for their review.

For data collection, the research facility utilizes an electronic data capture system, RedCap to maintain 21 CFR Part 11 compliance and Good Clinical Practice (GCP) standards.

All research materials collected from participants will be labeled with a unique identifier. Participant names and phone numbers will be recorded on a master list for scheduling and payment purposes only and will be kept on a password protected server, approved for use by OUHSC for the storage of human subjects data and which can only be accessed by approved study personnel, separate from research data.

Smoking topography data (interpuff interval; total time smoking; inhalation volume) will be collected in real time during smoking through a mouthpiece of the Clinical Research Support System (CReSS; Borgwaldt KC, Richmond, VA), a transducer-based smoking topography data collection device. This data will be collected in electronic files coded with participant identification number. Exhaled carbon monoxide will be collected via a Bedfont Micro+Smokerlyzer Monitor or an iCO Smokerlyzer (Covita), and measured in parts per million (ppm) immediately before and 10 minutes after laboratory or virtual smoking.

Information Withheld from Participants

During participant recruitment, individuals will be informed about the general requirements of the study but will not be informed about the specific inclusion/exclusion criteria to avoid them tailoring their responses to enter the study. Participants will not be informed of the specific objective of examining menthol's subjective effects to avoid influencing their perceptions and responses to smoking. It is very

important for the behavioral health research, not to tell them upfront about the study because then they will change their behavior towards the study and it will affect the study as well as the data. All participants will be debriefed when they complete the study. Participants will be offered option to withdraw their data being used.

Data Analysis Plan

Phase 1/Aim 1 Analyses

Primary Outcomes: (a) the absolute reinforcing value (ARV) of menthol cigarettes from Visit 1, **(b)** the relative reinforcing value (RRV) of menthol cigarettes from Visit/Session 3 based on Choice Task responding; **(c)** RRV of own vs experimental brand based on price elasticity. ARV of menthol cigarettes will be operationalized as between subject differences in subjective ratings of menthol vs non-menthol cigarettes (satisfaction, reward, craving reduction, physical sensations) during the ad libitum smoking Visit. RRV will be measured by evaluating motivation to "work harder" for menthol versus non-menthol cigarette puffs or for one's own brand from Visit 3. This is operationalized by the highest trial (breakpoint) that a participant successfully works for a menthol vs nonmenthol cigarette puff (or for their own vs experimental brand). Higher values reflect greater RRV of menthol cigarettes relative to non-menthol cigarettes (or their own brand vs the experimental brand. RRV of own vs experimental brand will be operationalized as cross-price elasticity of demand which measures the responsiveness of the quantity of experimental cigarettes that are self-reported to changing prices of the preferred cigarette brand.

Secondary Outcomes: (a) Total number of responses for the menthol versus the non-menthol-cigarette on the choice task **(b)** CO boost; and **(c)** puff topography (number of menthol versus menthol cigarette puffs consumed, number of minutes smoked, interval between puffs). Exploratory analyses will compare ARV and RRV.

A 2 (menthol preference) X 2 cigarette type (usual brand versus experimental brand) mixed ANOVA will be conducted to examine main effects and interactions on the outcomes of interest. Models will examine cigarettes per day (CPD), nicotine dependence, race/ethnicity, gender, and age of smoking onset as potential covariates. Factors related to Phase 1 drop-out will be examined as potential covariates. If nicotine and CPD are collinear, the most significant predictor of the outcome will be retained in the model. Significant interactions will be followed up with individual contrasts of cell means using Fisher's Least Significant Difference tests. In exploratory analyses, a 2 (menthol preference) X 4 (race/ethnicity: White, Black, Other, Hispanic) between-subjects ANOVA and a 2 (menthol preference) x 2 (gender) between subject ANOVA will be conducted separately for the BL Visit to evaluate differential reactions to own brand cigarette smoking by race/ethnicity and by gender. Comparison of own brand/usual brand and experimental cigarette ratings will also be made to determine the perceived similarity of the experimental cigarette to one's own brand and as a function of gender and race/ethnicity. NOTE: We expect that ratings of appeal/reinforcement for the experimental cigarettes will be lower than ratings of appeal for usual brand. Ratings of experimental cigarettes will be examined as a potential covariate in Aim 3 models. Age of smoking initiation will also be examined as a potential covariate. Covariates with $p < .05$ will be retained in final models.

Phase 2/Aim 2 Analyses

Primary Outcomes: (a) within-day subjective response (craving reduction, satisfaction, psychological reward, physical sensations like throat grab) to the most recent cigarette smoked (menthol vs non-menthol); **(b)** betweenday subjective response.

Secondary Outcomes: **(a)** Aggregate ratings of subjective response (over the course of 14 days) by baseline menthol brand preference (at the person-level, rather than by day); **(b)** changes over the course of days (creating an average change score for each person); **(c)** within-person variability by calculating the standard deviation of daily cigarette reward, satisfaction, craving reduction, and throat hit ratings for each person; **(d)** cigarettes per day (within-day, over days); and **(e)** craving intensity (within-day, over days).

Patterns of missing data, attrition rates, distributional properties of dependent and other measures, and correlations among all measures will be assessed. We will control for potential variables related to missing data and utilize multiple imputation methods (expectation maximization algorithm. Analysis of EMA data will use hierarchical linear modeling (HLM, which provides flexibility in handling missing data such that robust estimates can be obtained even when data are missing at random (MAR). Models for Aim 2 will examine effects of cigarette type (menthol vs non-menthol) at the day-level on predictions of subjective response (satisfaction, reward, craving reduction, physical sensations like throat grab) in that same smoking episode, and subjective response at time *t* (e.g., morning) predicting smoking behavior (number of cigarettes, any smoking, craving) occurring at subsequent points in time to determine the impact of subjective response on continued use by menthol status (controlling for cigarette consumption and subjective response from the previous report). A sub-group of respondents may have fixed (unchanging) ratings of subjective response over the course of 14 days, although this is unlikely given our pilot study data suggesting that daily subjective response varies significantly in this age group. We will examine baseline and daily factors that set "no changers" apart from those whose show fluctuations in subjective response. These factors will be used as covariates in models. Within-person slopes capturing associations between cigarette type and subjective response will be saved and used in Aim 3 regression models to predict 6-month smoking outcomes. Covariates with $p < .05$ will be retained in final models.

Analyses will control for the order in which study phases were completed (e.g., Phase 1 vs Phase 2 first).

Phase 3/Aim 3 Analyses

Primary Outcomes: (a) number of days smoked cigarettes in the past 30-days, **(b)** number of cigarettes smoked in the past 30-days, **(c)** nicotine dependence; and **(d)** continuous ratings of harm perceptions (relative and absolute). **Secondary Outcomes**: **(a)** number and use of non-cigarette tobacco products used in the past 30-days (or onset of use of non-cigarette tobacco product use, if none at baseline), **(b)** number and use of non-cigarette flavored tobacco products in the past 30-days (including assessment of type of flavor used, like candy, fruit, alcohol, etc); and **(c)** intentions to use menthol cigarettes (among non-menthol smokers). Intentions to use menthol cigarettes will also be assessed at follow-up among those reporting non-menthol as their preferred brand at baseline, using a modified 3-item algorithm: (1) "Do you think that you will try a menthol cigarette in the next 6-months? (2) "Do you think you will use a menthol cigarette anytime during the next month?" [we will assess next month and 6-months to increase variability]; (3) "If one of your best friends offered you a menthol cigarette, would you use it?" ("definitely yes," to "definitely not"). Because of a range of possible responses, intentions may change among some

participants, making it a reasonable outcome measure. It is possible that some YAs may stop smoking over the course of the 6-months. We will examine baseline, laboratory, and EMA findings that set these individuals apart from those who continue to smoke, as such information could be useful to FDA.

The main outcome analyses for Aim 3 will examine the predictive validity of laboratory (Phase 1) and EMA (Phase 2) outcomes on changes in the 6-month outcomes of interest, and the degree to which laboratory and EMA ratings of appeal/reinforcement account for (i.e., mediate) the association between menthol brand preference at baseline and smoking behavior change. Hierarchical regression models (continuous or binary logistic) will predict the 6-month outcome of interest, controlling for baseline levels of the outcome in interest and relevant demographics (gender, race/ethnicity, age of smoking onset) in Step 1, baseline menthol status in Step 2, and then laboratory or EMA-derived slopes Step 3. Models will be conducted separately using Phase 1 and Phase 2 measurements of appeal/reinforcement. Mediation will be reflected by a reduction in the association between baseline menthol preference and smoking outcomes after including the requisite measure of appeal/reinforcement in the model. Covariates with $p < .05$ will be retained in final models.

Exploratory analyses will examine changes over time in tobacco use behavior from baseline, 2,4, and 6-months. All data collected during the course of the study, survey and bio-specimen results, will be maintained for future use in cross-reference against new and continued data collection.

Human Subjects Protection

Potential Risks

Participants will not be exposed to any more risk than the usual risk they expose themselves to by choosing to smoke. Questionnaires and carbon monoxide measurement are all non-invasive and involve minimal risk to study participants. According to new statute passed in in early 2020, tobacco products, including Camel Crush cigarettes, are available in convenience stores to persons 21 years of age and older. 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. Participants who are under the age of 21 are still eligible to participate in the study, but will complete a modified version of the study protocol. They will complete the usual smoking session (e.g., lab session 1), the EMA, and follow-ups, but they will not be given experimental cigarettes until or unless we have approval to do so from the authorities. The PI is working with the OUHSC Office of Legal Counsel to obtain a waiver from the Oklahoma Attorney General that would allow us to provide cigarettes to individuals under the age of 21 for research purposes. Once we have approval, the IRB will be notified and we will proceed with sessions 2 and 3 and of the proposed study with individuals ages 18 to 20.

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 counseling.

Protection Against Risks

Risk of smoking cigarettes. The risk of side effects and adverse events are moderate to low. The cigarettes smoked during the course of this study will be either the participant's own brand provided by the participant, or a Camel Crush cigarettes. These products are sold online and at convenience and specialty stores nationwide. Although smoking is associated with disease, we do not expect the disease risk to be significantly greater from smoking the study cigarette. Participants will be told that they have the right to drop out of the study at any time and will be paid for what they have completed up to that point. They will also be informed that smoking is dangerous for one's health, but that the smoking involved in the study poses no more harm than their usual smoking exposure. At the end of the study, or upon request, participants will be given a list of resources to assist them to quit smoking should they be interested.

All participants will be: 1) screened for general medical precautions (pregnancy via urine dip stick test for females, asking for history of CF, COPD, asthma, and heart or lung disease) and 2) monitored for adverse events during the study period. Study personnel will assess for adverse events via self-report at all inperson visits. Participants will also be provided a study phone line to report an adverse event between visits. Any adverse events will be reported to the PI and then to the OUHSC IRB. The likelihood of an adverse (potential for nicotine overdose) event is low (< 1% in studies in our laboratory), and mild (nausea, headache), and will be handled quickly (i.e., advice to participants to reduce or stop tobacco use).

Loss of confidentiality and privacy. Confidentiality will be maintained by numerically coding all data, disguising identifying information, and keeping data locked in file drawers. Names and contact information of participants, including when collected during the telephone screen, will be kept in a separate locked drawer or file from participant data and can only be accessed by approved study personnel. Only research staff and the PI will have the information that connects participants' names and ID numbers. All electronic data will be numerically coded and stored on a password protected computer in a secure research space and this data will be kept separate from personally identifiable information. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical reporting in any publication. No personal information, other than the participant's name, will be collected in the eIC. As a result of these practices, it is unlikely that any loss of privacy will occur during the course of the study.

The following features are designed to ensure the security of the data of the mobile app that will be used for EMA data collection in Phase 2: 1) the data stored on the smartphone device are in a SQLite database in a sandbox environment, where read/write operations are only available through the programming application (i.e., no file or output is readable to end users); 2) a unique password (only known to researchers) is required to authenticate the current user before data can be manually accessed; 3) the web browser application linking the investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption) which will guarantee the data transfer from web browser to the backend database is well protected; and, 4) the backend database is hosted by Microsoft Azure and the University of Oklahoma Health Sciences Center (OUHSC). Azure has been approved by OUHSC risk assessment. The only personnel who have access to the Azure services are the mHealth developers. Study members have access to participant data through specified roles with secure logins and can only access data for their own projects. Azure databases are encrypted. Further, the data associated with the mobile app is

encrypted. Azure uses TDE (transparent data encryption) AES_256. The database on the app-related phone is encrypted with SQL-Cipher, which also underwent risk assessment and was approved for use by OUHSC. The OUHSC SSL certification for https encrypts data in transit. They only data that will be downloaded is data that can be accessed by the Battelle research team. Only research team personnel with specific roles can log in and download data. These steps will ensure the security of EMA data. Software will be downloaded onto each study phone so that phones can be remotely wiped if lost or stolen.

A Federal Certificate of Confidentiality is automatically provided by the NIH to protect against disclosures or release of data. All research personnel associated with this study have completed the Human Subject Protection Training Program or a training program approved by OUHSC. These are standard procedures used by PI of this application and they have been effective in the past.

Nicotine Withdrawal. Participants will be instructed to abstain from cigarette smoking for a minimum of 12 hours prior to each of the three visits in Phase 1. Some participants may experience nicotine withdrawal symptoms including irritability, difficulty concentrating, restlessness, anxiety, and depressed mood. Nicotine withdrawal symptoms can be uncomfortable, but they are not dangerous. Participants will be given information about the possibility of nicotine withdrawal symptoms at the end of the screening (before they attend the first baseline Visit) and again during the consent process.

Data Safety Monitoring Plan
Access to Identifiable Information and Data Storage:
Only research assistants who have completed training in the ethical conduct of research and the study PI (Dr. Cohn) will have access to individual identifiable private information about human subjects. All data (including survey responses) will be treated as confidential and identified only with a unique ID number and will never be stored or reported in association with identifying information. Participants will be assigned a subject ID number with results stored on a secure server with only study personnel having access to the data. Research data will be kept separate from personally identifiable information. Personally identifiable information will be kept in a separate database that will be stored on a password protected server that can only be accessed by approves study personnel. The Research Electronic Data Capture (REDCap) will be used to administer all questionnaires. REDCap is a secure, web-based application designed to support data capture and utilizes a computer-administered self-interview format. This system is designed to comply with all HIPAA regulations. REDCap e-signature is compliant with FDA 21 CFR Part 11.

Loss of Confidentiality and Privacy:
Confidentiality will be maintained by numerically coding all data, disguising identifying information, and keeping any hardcopy data locked in file drawers. Names of participants will be kept in a separate locked drawered from participant data. Only study research assistants and the PI will have the information that connects participant's name and ID number. All electronic data will be numerically coded and scored on a password protected computer in a secure research space. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical conduct of research (i.e., both HIPAA and CITI training). Identifying information will not be reported in any publication.

This is a low-risk observational study and we do not anticipate any Serious Adverse Events. Because a Data and Safety Monitoring Board is only required for higher risk and/or multisite studies, and the proposed research is a single site study with minimal risk, a formal Data and Safety Monitoring Board formed is not required. We do, however, have a detailed data and safety monitoring plan. Adverse events will be assessed by research personnel at each study visit via participant self-report and managed immediately. All serious adverse events will be reported to the OUHSC IRB.

We will monitor for risk of using cigarettes by screening participants via self-report for general medical precautions (pregnancy, cardiovascular disease). The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (< 1%) and mild (nausea, headache) and will be handled quickly (i.e., advice to participant to reduce or eliminate cigarette use). The PI will be available for any questions that participants may have about smoking, or smoking cessation. Participants will be given contact numbers of the laboratory and PI. Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be discussed immediately with the PI (Dr. Cohn). Dr. Cohn, or a delegate (Project Manager) will be responsible for completing an Adverse Events Form should an event occur. The Adverse Events Form will be reviewed by the PI and will report Serious Adverse Events to the OUHSC IRB within 24 hours of having received notice of the event. Dr. Cohn will gather any information needed to investigate the event and to determine subsequent action. Any subsequent action will be documented and reported to the OUHSC IRB.

Potential benefits of the proposed research to participants

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

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