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Title: The Interaction of Flavor with Nicotine Form in Adult Smokers

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
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Protocol Title: The interaction of flavor with nicotine form in adult smokers

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(*If applicable*) Clinicaltrials.gov Registration #: Click or tap here to enter text.

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

TCORS menthol Pilot Study

This proposal seeks to elucidate the impact of flavor (tobacco vs menthol) on reward/appeal, harshness/irritation and nicotine delivery from e-cigarettes containing nicotine (36mg/ml nicotine salt vs 36mg/ml free base nicotine e-liquids) in adult menthol smokers.

Primary Aim: Examine the influence of menthol flavor (when compared to a control tobacco flavor) on the effects of nicotine (freebase vs salt) on harshness/irritation and reward among menthol smokers. Participants will rate irritation/harshness using the General Labeled Magnitude Scale (gLMS)[1], reward (liking and wanting of drug effects) using the Revised Drug Effects Questionnaire (DEQ) [2] and liking/disliking of e-cigarette flavor using the Labeled Hedonic Scale (LHS)[3]. We hypothesize that menthol's effects on reduction of irritation will be greater following exposure to freebase nicotine e-liquids, when compared with nicotine salt. We also hypothesize that menthol when combined with nicotine salts will produce greater reward than when combined with freebase nicotine.

Secondary Aim: Examine the influence of menthol flavor on the effects of nicotine (freebase vs salt) stimulation, craving reduction, and alleviation of nicotine withdrawal. Participants will rate nicotine withdrawal and stimulation using the Revised DEQ and cigarette craving using the gLMS.

Exploratory Aim: Examine nicotine delivery following exposure to nicotine salt vs freebase nicotine exposure in combination with flavors (tobacco or menthol) by measuring saliva nicotine levels 5 min prior and 5, 15, 30, 45, and 55 minutes after nicotine and flavor exposure via e-cigarettes

K01 metabolism study

Eighty-Five African Americans (43 F,42 M) who smoke and have experience with e-cigarettes will participate in a double-blind, randomized, cross-over study across two experimental sessions. Following overnight abstinence from combustible tobacco products (CO≤10 ppm), participants will be randomly assigned to receive an e-cigarette with menthol flavor or control tobacco flavor (both in a concentration of 5% nicotine) on two separate days. Each session will consist of 1 puffing bout (10 puffs, 3 sec each puff, 30 sec puff interval) followed by 2 hours of abstinence, then 60 minutes of ad libitum e-cigarette use. The specific aims are:

Aim 1: Investigate the relationship of menthol flavor (vs tobacco flavor) and nicotine metabolite ratio (NMR) on nicotine pharmacokinetics and subjective effects during directed e-cigarette administration in African Americans who smoke. We hypothesize that during the menthol exposure session participants will have higher plasma nicotine levels compared to the tobacco flavor exposure session. We hypothesize that NMR is negatively associated with nicotine plasma levels during the tobacco flavor exposure sessions. Lastly, we hypothesize that participants will have a larger reduction of cigarette craving in the menthol compared to tobacco session. Primary outcomes: plasma nicotine boost, nicotine area under the curve. Secondary outcome: cigarette craving. Exploratory outcomes: other subjective effects such as liking of e-cig taste. Gender differences will be explored for all outcomes.

Aim 2: Elucidate the relationship between menthol flavor (vs tobacco flavor) and NMR on nicotine pharmacokinetics and subjective effects during e-cigarette ad libitum use in African Americans who smoke. We hypothesize that participants will take more puffs during the menthol session compared to the tobacco session. Additionally, we hypothesize that participants will titrate their nicotine intake and have similar nicotine plasma levels for both flavor exposure sessions. Furthermore,

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we hypothesize that NMR will be positively associated with nicotine delivery (amount of e-liquid used x nicotine e-liquid concentration) for both flavor sessions. Lastly, we hypothesize that participants will have a larger reduction of cigarette craving in the menthol compared to tobacco session. Primary outcomes: plasma nicotine boost, nicotine area under the curve. Secondary outcomes: measure of nicotine delivered to participant and cigarette craving. Exploratory outcomes: number of puffs and subjective effects. Gender differences will be explored for all outcomes.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   2 years

   TCORS Menthol Pilot Study

Study	Quarter 1	Quarter 2	Quarter 3	Quarter 4
2 experiment sessions	7 completers	7 completers	8 completers Analyze results.	8 completers Analyze results. Present at conference. Publish

   K01 Metabolism Study
   I anticipate completing both phases of the study by the end of this 5-year K01 award (funded Sept 2020). I anticipate completing 21 participants per year.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   TCORS Menthol Pilot Study

   Combustible tobacco product use contributes to 90% of lung cancer cases and 500,000 other related deaths per year in the United States[4]. In particular, menthol cigarette smokers have greater nicotine dependence [5] and have lower cessation rates than non-menthol cigarette smokers [6]. Electronic(e-) cigarette devices, which have been shown to be acutely less harmful than cigarettes[7], may serve as harm reduction tools [8]. Smokers transitioning to e-cigarettes completely may reduce the health burdens associated with tobacco use disorder[4]. Given that smoking is reinforced by nicotine dependence[9], it is critical to understand which form of nicotine in e-cigarettes is important to established menthol smokers and will aid in their transition to e-cigarettes.

   Pod e-cigarette devices such as the JUUL have surged in popularity in the past year [10] and introduced nicotine salts into the e-cigarette/e-liquid market. Prior to this entrance, freebase nicotine was the only form of nicotine found in e-liquids. Compared to nicotine salts, freebase nicotine is thought to cause greater irritation/harshness at high doses [11,12]. In addition, e-cigarette companies have suggested that nicotine salts deliver more nicotine to the user than freebase nicotine [13,14]. However, we lack empirical evidence on both these issues. Further, e-cigarette/e-liquid companies market nicotine salts in e-liquids as an avenue for established smokers to transition to e-cigarettes. However, the rewarding effects of nicotine salts vs freebase nicotine have not been tested in smokers.

   Flavors are known to play a significant role in increasing the appeal of tobacco and nicotine products[15–17]. Menthol is one such flavor which is present in both e-cigarettes that contain freebase nicotine and those that contain nicotine salts. Menthol is thought to reduce the harshness and

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irritation of nicotine [18–20]. Thus, menthol's effect on harshness may differ depending on the form of nicotine present in e-liquids because, as discussed earlier, nicotine freebase and nicotine salt may have differential irritant properties. Furthermore, given that previous studies have shown that irritation/harshness of e-liquids negatively correlates with reward/appeal[21], menthol may also have divergent effects on reward of freebase nicotine and nicotine salt e-liquids. Therefore, this proposal seeks to investigate the effect of menthol flavor on nicotine salt vs freebase nicotine e-liquids on irritation/harshness, reward and nicotine delivery in adult smokers. Since the appeal of mentholated nicotine products may be particularly relevant for menthol smokers, who are also known to have more difficulty quitting smoking[6,22], we will conduct this examination in menthol smokers

K01 Metabolism Study

The overall goal of this proposal is to understand the relationship between menthol e-liquid flavor (vs tobacco e-liquid flavor) and nicotine metabolite ratio (NMR) on plasma pharmacokinetic parameters of nicotine and subjective effects in African Americans who smoke. This proposal will utilize two lab-based e-cigarette exposure paradigms: (A) directed e-cigarette administration and (B) e-cigarette ad libitum use. The following aims will be investigated: (1): Investigate the relationship of menthol flavor(vs tobacco flavor) and NMR on nicotine pharmacokinetics and subjective effects during directed e-cigarette administration and (2): Elucidate the relationship between menthol flavor and NMR on nicotine pharmacokinetics and subjective effects during e-cigarette ad libitum use.

African Americans are disproportionately burdened with tobacco-related health diseases compared to other racial groups in the US [23,24]. African Americans who smoke are more likely to develop lung cancer compared to smokers of other ethnic/racial groups[25,26]. These health disparities exist even though African Americans are more likely to be light smokers (smoke less than 10 cigarettes per day)[27,28] and less likely to be daily smokers [29,30]. African Americans also take in more nicotine when smoking compared to White people who smoke [31]. The more intense smoking by African Americans may be related to the observation that 80% of African Americans who smoke are menthol smokers[5,32]. Menthol has cooling and analgesic properties via the transient receptor potential channels [33,34], which may reduce irritation from tobacco smoke and nicotine [18,35] **Menthol cigarettes pose a greater public health risk than non-menthol cigarettes because those who use menthol cigarettes have higher nicotine dependence** [5,36–38] **and decreased success in quitting smoking**[37,39]**.**

It is important to understand the role of menthol flavor in nicotine dependence in African Americans. Nicotine, a compound found in tobacco products, activates nicotinic acetylcholine receptors in the mesolimbic pathway to induce rewarding and reinforcing properties [40]. Constituents of tobacco products that have an influence on nicotine levels may influence dependence and addiction of tobacco products. Preclinical studies suggest that menthol inhibits nicotine metabolism[41] by inhibiting the enzyme primarily responsible for the metabolism of nicotine through oxidation, CYP2A6[42]. Additionally, studies have also shown that African Americans who smoke have a slower nicotine metabolism than White people who smoke [31,43,44]. African Americans who smoke have been shown to have slower oxidative metabolism of nicotine and slower N-glucuronidation than White people who smoke[45]. However, since 80% of African Americans who smoke, smoke menthol cigarettes, it is unclear if the effect on nicotine metabolism in African Americans is the result of menthol exposure. Furthermore, there are few studies that have investigated the differential impact of menthol on nicotine metabolism within the African American population. Additionally, It has been shown that females who smoke are more likely to smoke menthol cigarettes compared to men, however gender differences within Black people who smoke is understudied[46].

Electronic (e)-cigarettes are an ideal system for examining the inhaled effects of menthol on nicotine metabolism in African Americans who smoke. E-cigarettes are battery operated devices that heat e-liquids containing nicotine, flavors and other constituents such as propylene glycol and glycerin [47]. E-cigarettes have a similar route of nicotine administration to cigarettes and there are similar habitual smoking-related behaviors (hand to mouth movements)[8]. A previous clinical intervention study

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conducted suggested that menthol in cigarettes reduces nicotine metabolism in White and African Americans who smoke [48]. Further supporting menthol's potential role on nicotine metabolism, a survey study that collected NMR in White, Filipinos and Native Hawaiians showed that those who smoked menthol cigarettes had a slower metabolism than those who smoked non-menthol cigarettes [49,50]However, given that cigarettes contain hundreds of chemicals, e-cigarettes are an ideal tobacco product to test the impact of menthol on nicotine metabolism. Additionally, there have been limited examinations of the influence of e-cigarettes in African Americans who smoke. To our knowledge, there are only two outpatient studies that experimentally examined toxicant exposure and subjective effects of e-cigarettes among African Americans[51,52]. There are no lab-based experimental e-cigarette administration studies that investigate the impact of menthol on the pharmacokinetic effects of nicotine via e-cigarettes within an in African American sample. African Americans are underrepresented in tobacco research even though they carry a disproportionate burden of tobacco related diseases. Intentional efforts are needed to correct this. Therefore, this proposal will recruitment African Americans who smoke which will aid in reducing tobacco-related health burdens in African Americans and benefit overall public health.

Tobacco Regulatory Impact of Proposed Research: This proposal will provide additional scientific data to inform regulation of tobacco products by addressing the FDA's Behavior and Addiction scientific interest areas and focus on Africans Americans which represent a vulnerable population. **Behavior** – this proposal seeks to understand the knowledge, attitudes, and behaviors related to use of menthol tobacco products in African Americans. **Addiction**- this application will understand the impact of menthol on nicotine metabolism and dependence in individuals who smoke. **Vulnerable population**- this application could aid in reducing tobacco-related health burdens in African Americans which would benefit overall public health.

The scientific premise for this proposal is to address critical gaps in menthol flavor research by evaluating the impact of menthol and NMR on nicotine pharmacokinetics and subjective in e-cigarettes among African Americans who smoke.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

TCORS menthol pilot study

Uses:
Suorin iShare e-cigarette
DuraSmoke® brand Tobacco Virginia e-liquid, 36 mg/mL nicotine (salt equivalent)
AmericaneLiquid® brand Tobacco-Menthol e-liquid, 36 mg/mL nicotine
DuraSmoke® brand Tobacco Menthol e-liquid, 36 mg/mL nicotine (salt equivalent)
AmericaneLiquid® brand Tobacco-Virginia e-liquid, 36 mg/mL nicotine

This is a double-blind study. Subjects will be blinded to the form of nicotine (salt vs freebase) and the flavor (menthol vs tobacco flavor).

Experimental design: This proposal seeks to elucidate the differences in reward/appeal, harshness/irritation, nicotine delivery, preference and impact of menthol flavor (compared to control tobacco flavor) between nicotine salt vs free base nicotine e-liquids. Thirty adult menthol smokers (15 male; 15 female) will participate in a double-blind, randomized, cross-over study across three experimental sessions. For the first two sessions, each participant will be randomly assigned to receive nicotine salt or freebase nicotine (both in a concentration of 36mg/ml) on two separate days (see Table 1). Freebase nicotine e-liquid at concentration of 36mg/ml has been used previously in

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smokers with no reported adverse effects [53,54] and this concentration is within range of nicotine concentrations used in nicotine salt e-liquids/e-cigarette pod devices [55,56]. Following overnight abstinence from combustible tobacco products (CO≤10 ppm), participants will be exposed to the assigned form of nicotine in combination with two flavor conditions (tobacco and menthol) in a counterbalanced randomized order. Each exposure will consist of 2 2-sec puffs and will be separated by a 60-minute washout period (see Table 2).

iSaliva nicotine/ cotinine is an exploratory outcome and nicotine/cotinine levels will be assessed using saliva samples obtained 10 times per session (5 min prior to and 5, 15, 30, 45, and 55 minutes after the onset of puff1, and 5, 15, 30, and 45 minutes after the onset of puff2). Assessing the nicotine/cotinine levels will determine if there are pharmacokinetic differences between nicotine salts vs freebase nicotine. After completing the first two e-cigarette exposure sessions, the same thirty adult menthol smokers (15 female, 15 male) will undergo overnight abstinence from combustible tobacco and nicotine products and participant in a 60-minute choice e-cigarette self-administration session.
During the third session, each participant will then be exposed to the same e-liquids they were exposed to during the two experimental sessions. During the third session participants can freely self-administer any of the four e-liquids in an e-cigarette pod device (see Table 3). Participants will be left alone in the room to use all four of the e-cigarettes in any order or frequency they choose (Table 1). The third session will be video recorded. This session will be double blinded but to ensure participants distinguish each e-cigarette from each other, the e-cigarettes will be labeled with letters A, B, C, D randomly by a research assistant who is not conducting the study or coding the videos. This labeling will also be helpful for the video coders so they can distinguish e-cigarettes. E-liquids will be measured before and after the session. Two research assistants will independently code the video-tapes for puffing behaviors. Heart rate and blood pressure will be monitored throughout the session for safety, and participants will be told that they can stop anytime if they feel uncomfortable. Per the current practice of Dr. Krishnan-Sarin's research group, participants will be trained on how to puff the e-cigarettes, prior to the self-administration session. Training will be conducted using e-cigarettes that contain the base liquid of 50% propylene glycol(PG)/50% vegetable glycerin(VG).

The third session will be videotaped to ensure experimenter reliability, and to review individual participant's vaping. The commercially available Suorin iShare ™ and commercially available e-liquids will be used for our studies. The Suorin iShare ™ is a refillable pod system e-cigarette device composed of a battery without voltage control and a refillable pod that contains the e-liquid, mouthpiece and coil. It is among one of the pod e-cigarette devices that are used widely[57,58]. Participants will not be allowed to keep the device. One month after the third session, participants will receive a follow up phone call to assess any health symptoms via a health assessment list, fatigue and shortness of breath.

For the safety of participants, we will add plexiglass dividers in the rooms where experimental sessions take place to limit contact between participants and researchers. To limit in-person interactions during experimental sessions, we will give instructions and communicate to participants from another location remotely using a 2-way audio system. Hand sanitizer will be available, and participants will be asked to wear gloves for the duration of the lab session. All devices and areas will be sanitized before and after each participant. These changes have been added to the protocol and consent.

Table 1: Four e-cigarettes conditions that will be used throughout the study.

Nicotine Concentration	Nicotine Condition	Flavor
36mg/ml	**salt**	**tobacco**

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36mg/ml	**salt**	**menthol**
36mg/ml	**freebase**	**tobacco**
36mg/ml	**freebase**	**menthol**

Table 2: First Two Experimental Sessions Breakdown: Each session participants will be exposed to two separate conditions (see table 3). Below is an example of one session.

• Assessments • Saliva collection (1 sample) • CO	1st Directed Puff (e-cig condition from table 3)	Nicotine washout period • Assessments • Saliva collection (5 samples)	2nd Directed puff (a different e-cig condition from table 3	Nicotine washout period • Assessments • Saliva collection (4 samples)
5 min		5 min		60 min

Table 3:
Third experimental session design breakdown. 60-minute e-cigarette self-administration

• Weigh e-liquids • CO	Self-administration (ad-lib) [all four of the e-cigarette conditions in Table 3 that participants were exposed to in the Yale TCORS sessions]	• Weigh e-liquids
5 min	60 min	5 min

K01 metabolism study
Uses Juul Device
Menthol eLiquid 59mg/ml (5%) nicotine
Virginia Tobacco eLiquid 59mg/ml (5%) nicotine

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Aim 1: Investigate the relationship of menthol flavor (vs tobacco flavor) and NMR on nicotine pharmacokinetics and subjective effects during directed e-cigarette administration.

Experimental Design: Aim 1 focuses on the directed e-cigarette administration procedure. Saliva NMR will be assessed at intake appointment and will be a continuous measure in this study[59,60]. Following overnight abstinence from combustible tobacco products (CO≤10 ppm), African Americans who smoke will participant in a double-blind, counterbalanced and randomized e-cigarette exposure laboratory study where they will receive two e-liquid flavors (menthol, tobacco) with a fixed nicotine salt concentration in e-cigarettes (5%) on two separate days (one flavor condition per session). The directed e-cigarette administration procedure will consist of 1 fixed-puffing bout (puffing bout=10 puffs, 3 sec each puff, 30 sec puff interval) as done previously by my mentor, Dr. Krishnan-Sarin [61]. Per the procedures conducted by my co-mentor Dr. Benowitz's research group [62,63], plasma nicotine levels will be assessed at baseline and 5, 15, 30, 45 and 60 minutes after nicotine exposure via e-liquids during the directed e-cigarette administration procedure. Heart rate and blood pressure will be measured at 5, 15 and 30 minutes after the final puff. Participants will rate irritation/harshness, coolness, cigarette craving, e-cigarette craving, liking of e-cig taste, reward/appeal of e-cig, nicotine withdrawal and stimulation at baseline, 5 and 15 min after nicotine concentration exposure. Participants will be told that they can stop anytime if they feel uncomfortable. **Independent variables:** sex (male or female), nicotine metabolite ratio, flavor (menthol, tobacco), **Dependent variables**: primary outcomes- plasma nicotine boost, nicotine area under the curve; secondary outcomes- cigarette craving; exploratory outcomes- reward/appeal of e-cigs, e-cig craving, irritation/harshness, coolness, nicotine withdrawal, stimulation, liking of e-cig taste. We will explore gender differences for all outcomes.

Aim 2: Elucidate the relationship between menthol flavor (vs tobacco flavor) and NMR on nicotine pharmacokinetics and subjective effects during e-cigarette ad libitum use

Eligibility/ Recruitment/Screening: African Americans who participant in Aim 1 will participate in Aim 2.

Experimental Design Aim 2 focuses on the ad-lib e-cigarette exposure. Saliva NMR will be assessed at intake appointment. For each lab session, 120 min after the directed e-cigarette exposure period (Aim 1) participants will undergo a 60 min ad-lib e-cigarette exposure session. For each lab session, each participant will be exposed to the same JUULpods they were exposed to during the directed e-cigarette exposure period. During the ad-lib e-cigarette period, participants can freely self-administer the e-cigarette. The ad-lib period will be video recorded to record puffing behaviors. E-liquids will be measured before and after the session. Two research assistants will independently code the videotapes for puffing behaviors. Participants will be told that they can stop anytime if they feel uncomfortable. Plasma nicotine levels will be assessed at baseline and 15, 30 and 60 minutes after the start of the ad-lib e-cigarette exposure period. Participants will be told that they can stop anytime if they feel uncomfortable. Smoking cessation materials/programs will be offered at the end of the study. **Independent variables:** sex (male or female), nicotine metabolite ratio, flavor (menthol, tobacco), **Dependent variables**: primary outcomes- plasma nicotine boost and nicotine area

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under the curve. Secondary outcomes- measure of nicotine delivered to participant and cigarette craving. exploratory outcomes- number of puffs and subjective effects as mentioned in Aim 1. We will explore gender differences for all outcomes

The JUUL ™ and menthol and tobacco JUUL pods™[5%(59mg/ml)] will be used for this study. The JUUL™ is one of the most widely used pod e-cigarette devices[57,58]. Participants will not be allowed to keep the device.

Figure 1: Study Experimental Design

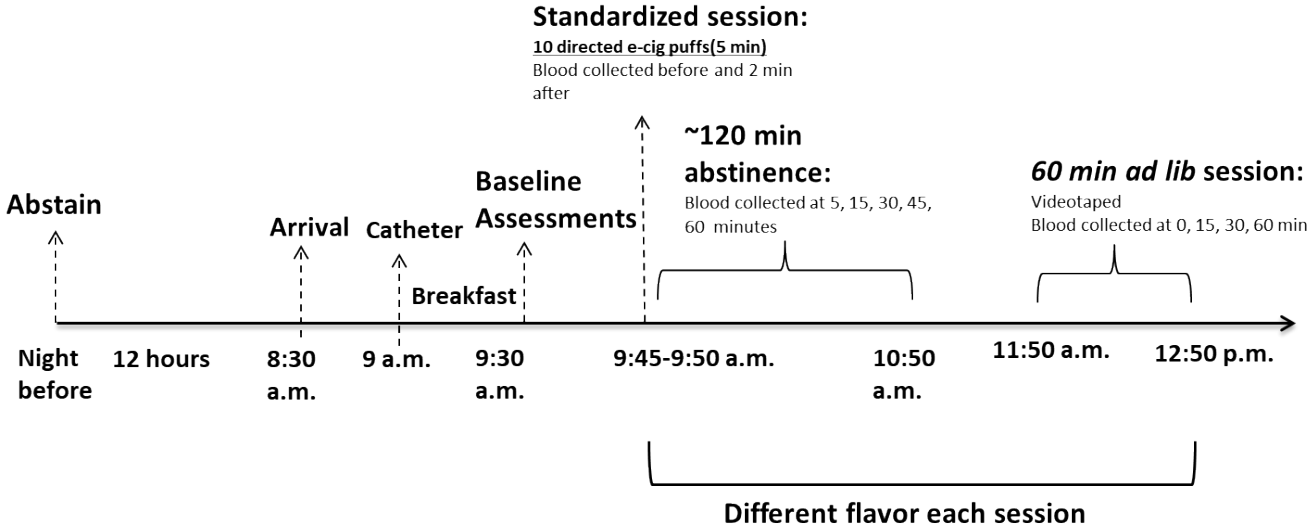

Figure 1 Legend: Depicts the time for each lab session. Participants will undergo two lab sessions. Participants will receive two e-liquid flavors (menthol, tobacco) with a fixed nicotine salt concentration in e-cigs (5%) on two separate days (one flavor condition per session).

Assessments

1. General Labeled Magnitude Scale (gLMS)(experimental sessions)[1]: For TCORS Menthol pilot, gLMS ratings will be obtained 5, 15, 30, 45, and 55 minutes after each puff during lab 1 and lab 2. Participants will rate coolness, irritation/harshness, cigarette and e-cigarette craving using the gLMS which is a category ratio scale with 7 semantic labels: “no sensation”, “barely detectable”, “weak”, “moderate”, “strong”, “very strong”, and “strongest imaginable”. The labels are positioned quasi-logarithmically according to their empirically determined semantic magnitudes. The gLMS will be displayed on a monitor via a custom LabView® program, and participants will make their ratings using a mouse. Ratings are numerically transformed and then used for statistical analyses. For the K01 metabolism study will be assess irritation/harshness, coolness, cigarette craving, e-

cig craving at baseline, 5 and 15 min after nicotine exposure during the directed puffing section of lab sessions.

2. Labeled Hedonic Scale (LHS)(experimental sessions)[3] : For TCORS Menthol pilot, liking of e-cigarette taste will be assessed 5 min after each flavor exposure using the LHS scale. The LHS is a bipolar scale with "neutral" in the middle and 5 symmetrical semantic labels: "like/dislike slightly", "like/dislike moderately", "like/dislike very much", "like/dislike extremely", "most liked/disliked imaginable", positioned on the scale according to their semantic magnitude. The LHS yields ratio-level data on the magnitude of liking/disliking of sensation equivalent to that produced by magnitude estimation (ME). This scale will also be displayed on a computer screen as above and numerically transformed.
   For K01 metabolism study, liking of e-cig taste will be assessed at baseline, 5 min and 15 min after nicotine exposure during the directed puffing section of lab sessions.
3. E-cig Effects (Adapted from Drug Effects Questionnaire (DEQ[61])(experimental sessions): A modified version of the Drug Effects Questionnaire will be used in which participants will rate acute responses to the e-cig on a 0 to 100 mm scale, from "not at all" to "extremely." 5, 15, 30, 45, and 55 minutes after each puffing, we will assess liking/wanting of drug effects (average of "I feel good e-cig effects", "I want more of that e-cig I received", "I feel the e-cig strength" and "I like the e-cig effect"), stimulant effects (average of "I feel energized" and "I feel high"), and nicotine withdrawal (average of "I feel sleepy", "I feel angry", "I feel irritable", "I am having difficulty concentrating", "I feel restless" and "I feel hungry").
   For K01 metabolism study, reward/appeal of e-cigs, nicotine withdrawal and stimulation will be assessed at baseline, 5 and 15 min after nicotine exposure during the directed puffing section of lab sessions.
4. Carbon Monoxide (CO) levels (experimental sessions): At intake we will assess recent smoking and participants with ≥10ppm will be included in the study for both studies. For lab sessions for both studies, CO levels in exhaled breath will be measured using a MicroCO breath CO monitor and levels of ≤10 ppm will be used to ensure abstinence prior to the experimental sessions.
5. Urine Cotinine levels: At intake for both studies, urine samples will be assessed with Alere iScreen OFD Cotinine urine test to verify eligibility.
6. Salivary nicotine and cotinine levels for TCORS menthol pilot study(experimental sessions): Saliva nicotine and cotinine levels will be monitored using saliva samples obtained 10 times per session (5 min prior to and 5, 15, 30, 45, and 55 minutes after the onset of puff1, and 5, 15, 30, and 45 minutes after the onset of puff 2). To try to avoid contamination from buccal nicotine, participants will be asked to rinse their mouths prior to providing each sample. These levels will be used for correlational analyses with behavioral measures and will be determined using LC/MS techniques at the core laboratory of the YCSTP.
7. Saliva nicotine metabolite ratio or NMR (trans 3'-hydrocotinine/ cotinine) for K01 metabolism study will be assessed through Yale TCORS. To try to avoid contamination from buccal nicotine, participants will be asked to rinse their mouths prior to providing each sample
8. Asthma Control Test(Intake): At intake for both studies, participants will be asked to rate their asthma symptoms on a 1-5 scale, from "all of the time" to "none of the time". This five question health survey is used to measure asthma control in individuals 12 years and older
9. Fatigue(all appointments): At all appointments for both studies, we will use the 7-item PROMIS measure of fatigue which rates fatigue from 1="never" to 5="always"..
10. Shortness of Breath (all appointments): At all appointments for both studies, we will use the 5-item PROMIS measure of dyspnea which rates shortness of breath from 1-10. Items include: shortness of breath in general, intensity of shortness of breath, frequency of shortness of breath and duration of shortness of breath.
11. Lung spirometry will be assessed for both studies at intake.

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12. Heart Rate, Blood Pressure, Pulse Oximetry (all appointments): For both studies, these measures will be assessed to monitor health status at baseline and throughout the study at each in-person visit. Heart rate and blood pressure will be assessed. Pulse oximetry is the measurement of the oxygen in the blood.
    For the K01 metabolism study, heart rate and blood pressure will be assessed at baseline 5, 15 and 30 min after nicotine exposure.
13. Health assessment checklist (all appointments): For both studies, we will also monitor checklist of health symptoms (e.g., headaches, dizziness, fainting, nausea, diarrhea) and severity of these symptoms that could be related to nicotine exposure/vaping illness at each in-person visit.

14. Demographic Information (At Intake): For both studies ,age, race, marital status, educational and occupational levels and medical history will be assessed with interviews and self-report forms.
15. Nicotine Dependence (At Intake): We will use the 8-item PROMIS measure of nicotine dependence developed for cigarettes [64] and which we have validated for e-cigs [65], which shows internal consistency & measurement invariance across sex and race.
16. Tobacco Use History Questionnaire (At Intake): For both studies, self-reports will be obtained from all participants; questions will be benchmarked to the NIDA PATH data.
17. Risk perceptions of e-cigs and cigarettes: *For both studies* we will assess baseline risk perceptions of e-cigs and cigarettes.
18. Flavor use history: For both studies we will assess the use of e-cig and cigarette flavors at intake.
19. Social determinants of health measures for K01 metabolism study will include assessments on employment status, education level, income, homeownership, experiences of discrimination, perceived neighborhood disadvantage, including problems (e.g., traffic, safety) and social cohesion and trust (e.g., connections, shared values, and willingness to help among neighbors) food security, utility needs, housing instability, transportation problems. These socioeconomic measures have been shown to be important predictors for tobacco use behaviors [66].
20. Timeline Follow Back Interview(all appointments)[67,68]: For both studies, we will use of cigarettes, little cigars and e-cigs (with or without nicotine) will be examined using a 30-day TLFB at intake and experimental sessions. Test-retest reliability is high in adult smokers, and we have used it with younger smokers.
21. The amount of e-liquid used from each e-cigarette will be measured before and after the e-cigarette self-administration session for both studies.
22. Puffing behavior will be assessed by the number of puffs, and time to first puff for each of the four e-cigarettes in the self-administration session for both studies. Two research assistants will independently code the video-tapes for puffing behaviors which will then be averaged across raters.
23. Physical function scale will select individuals who have good physical functioning. As part of the medical history, the following 4 PROMIS questions will be asked: Are you able to do chores such as vacuuming or yard work? Are you able to go up and down stairs at a normal pace? Are you able to go for a walk of at least 15 minutes? Are you able to run errands and shop? Response options for these questions are “Without any difficulty”, “With a little difficulty”, “With some difficulty”, “With much difficulty” and “Unable to do so” (Beidelschies et al 2019). To be eligible, participants must respond “Without any difficulty” to all 4 questions. We assess this for both studies at every appointment.
24. Urine drug and pregnancy tests: Urine drug screen will assess recent drug use at intake for both studies. If participants test positive for any drugs except marijuana and drugs they are not prescribed at the in-person intake appointment, they will not be paid for the visit and will have the opportunity to reschedule this appointment one time. Urine drug screen assesses benzodiazepines, marijuana, methadone, cocaine, methamphetamine, morphine, MDMA, oxycodone, barbiturates, buprenorphine, amphetamine phencyclidine, methadone metabolites,

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tricyclic antidepressants and propoxyphene. We will administer pregnancy tests to all female participants at baseline and every vaping session appointment while they are enrolled in the study. In addition, female enrollees will be verbally asked about their pregnancy risk (such as unprotected sex or a missed menstrual period).

25. Plasma nicotine levels for K01 metabolism study will be assessed using blood samples obtained at baseline and 5, 15, 30, 45, 60 minutes after nicotine exposure during the directed e-cigarette portion and plasma nicotine levels will be assessed using blood samples obtained at baseline and 15, 30, 60 minutes after nicotine exposure during ad-lib session. 60 ml of blood will be drawn at each e-cigarette exposure through insertion of an intravenous catheter during e-cigarette directed administration session (total of 120ml for all laboratory session in study or 8 tablespoons) which is below the IRB guidelines of 450 ml within eight research weeks. We will recommend participants wait at least 4 weeks to donate blood. We will then calculate the nicotine boost and the area under the curve. These levels will be determined using LC/MS techniques through the Yale TCORS Lab and Analytical Core.
26. Amount of nicotine delivered to participants will be assessed for K01 metabolism study. The amount of e-liquid in pods will be measured before and after the ad-lib e-cigarette exposure period. We will then multiply the amount of e-liquid used by the nicotine concentration of the e-liquid (5%) to calculate the amount of nicotine delivered to the participants[62].

5. Genetic Testing N/A ☒

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

TCORS menthol pilot study

30 healthy participants will ≥21 years of age; smoking menthol cigarettes/cigars/little cigars at least 5 per day, with CO levels ≥10 ppm and have ≥ 3 on the urine NicAlert test, willing to abstain from all combustible tobacco products 12 hrs prior to each experimental session, not currently planning to stop smoking, limited experience with e-cigs (not more than 25 times lifetime).

K01 metabolism study

Eighty-five healthy African American participants (43 female and 42 males who smoke) who are ≥21 years of age; able to read and write English, smoking at least 5 menthol cigarettes per day on at least 25 days or more in past month[69,70], CO≥10 ppm and provide a semi-quantitative urine cotinine result of at least 200 ng/ml assessed with Alere iScreen OFD Cotinine, willing to abstain from tobacco and nicotine products 12 hrs. prior to each lab session, used e-cigarettes at least 10 times in the past six months, do not plan to quit e-cigarette use, not planning a smoking quit attempt ,have not stopped e-cigarette use due to COVID, willing to try e-cigarettes for the study, must report ever JUUL use and/or other nicotine salt/pod e-cigarette devices (i.e., JUUL-like), report regular menthol cigarette use

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children ☐ Healthy ☐Fetal material, placenta, or dead fetus

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☐Non-English Speaking ☐ Prisoners ☐Economically disadvantaged persons
☐Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses
☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

CORE INCLUSION/EXCLUSION CRITERIA FOR BOTH STUDIES:

Inclusion:
- At least 21 years of age
- Able to read and write English.
- Smoking at least 5 menthol cigarettes/cigars/little cigars per day
- Report regular menthol cigarette use
- CO≥10 ppm and have at least 200ng/ml urine cotinine
- Willing to abstain from combustible tobacco products 12 hrs prior to each experimental session.
- not planning a smoking quit attempt.
- Have not stopped use due to COVID.
- used e-cigarettes at least 10 times in the past six months.
- Fully vaccinated against COVID-19.

Exclusions:
- Use of psychoactive drugs including anxiolytics, antidepressants, and other psychostimulants unless prescribed and stable for two months.
- Current diagnosis of any severe psychiatric disorder
- Any significant current medical condition such as neurological, cardiovascular, endocrine, renal, pulmonary or hepatic pathology that would increase risk or would interfere with/mimic tobacco abstinence.
- Known hypersensitivity to propylene glycol and nut allergies.
- Pregnant or lactating females.
- current criteria for moderate or severe cannabis and alcohol use disorder per DSM-5 criteria.
- current criteria for other substance use disorders per DSM-5 criteria.
- Seeking treatment to stop smoking.
- individuals who do not want to use e-cigarettes.
- Uncontrolled asthma (defined as <20 on Asthma Control Test) AND/OR endorsement of “yes” to environmentally induced bronchospasm that requires prescription Epipen)
- blood pressure >170/>100 and heart rate >100
- vaping of CBD/THC or marijuana related products in the past 3 months

- For current THC vapers: Any report of mild or great EVALI-related symptoms (i.e. cough, shortness of breath, chest pain, nausea, vomiting, stomach pain, diarrhea, fever, chills, or weight loss) without non-EVALI reasonable and proximal cause

K01 metabolism study-specific inclusion criteria:

1) African American

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2) must report history of JUUL and other nicotine salt/pod devices (i.e., JUUL-like)

9. How will **eligibility** be determined, and by whom?

Participants will have the option to sign informed consent via RedCap, through mail or in-person and complete initial assessments including medical and substance use histories for intake remotely or in-person. If eligible following administration of remote intake, participants will come in for a very brief visit in which biochemical measures will be collected: urine drug and pregnancy tests, breath CO, urine cotinine levels, saliva NMR, pulse oximetry readings, lung spirometry, heart rate and blood pressure. If participants do not wish or do not have the internet capabilities to participate in remote intake, the participants can also sign informed consent and assessments in person at Connecticut Mental Health Center.

During the duration of the study, participants will be given a questionnaire daily to assess COVID symptoms they may be experiencing. This survey is in line with Yale's Return to Campus Protocol (https://ypps.yale.edu/sites/default/files/files/StayHome.pdf). If yes is endorsed for any symptom, the research team will follow up via phone call and ask participant to describe symptoms and rate symptom severity. For any symptoms described as severe and unrelated to other causes (i.e. headache for someone who is abstaining from their normal caffeine, muscle pain related to a workout, symptoms of seasonal allergies), the research team will evaluate the symptoms with a study physician. Based on physician recommendation, study participation will be paused until a negative COVID test can be produced. All participants will be instructed to contact their doctor and/or get a COVID test under these conditions. This COVID symptom check survey will be started the day prior to the first in person lab session and will continue through completion of the ad-lib period. Participants will not be allowed to complete in person sessions unless the COVID symptom checks are completed. Once participant arrive at their appointment location, a COVID screening (including temperature and symptom check) will be conducted as part of their appointment. If a subject answers "yes" to any COVID screening question or has a temperature of ≥100˚F, their appointment must be discontinued, they must be escorted from the building to a separate isolation tent outside the facility (if appointment is at CMHC), and instructed to immediately contact their primary health care provide or call the Campus COVID Resource line (203-432-6604). At satellite sites at which research staff are themselves conducting primary symptom screening outside the building as described above, participants will not be escorted to an isolation tent, but instructed to immediately contact their primary health care provider or call the Campus COVID Resource line (203-432-6604).

If subject is suspected to be intoxicated at intake visit, a breathalyzer will be performed. If the BAC level is ≥ 0.05, we will ask the subject to remain in the clinic and we will repeat the breathalyzer periodically. During this time, medical procedures (e.g. urine, etc.) may be done based on the judgement of the provider; no self-report type assessments will be administered. The subject's BAC level must be <0.05 for subject to leave the clinic, otherwise a friend can be called, or other transportation can be arranged.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Experiencing nicotine withdrawal: During the abstinence period prior to the e-cigarette lab exposure sessions in Aim 1, participants may experience symptoms of nicotine withdrawal, such as nicotine craving, mild anxiety, restlessness, irritability, difficulty concentrating, loss of energy and excessive hunger. These

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are normal symptoms that people experience when they stop smoking and they can be uncomfortable, but they are not life threatening.
Breath, saliva and urine collections: Breath CO, saliva, and urine collections should add no risks other than those normally associated with these procedures.
Blood Drawing (K01 Metabolism only): Drawing blood is a safe and standard medical procedure. Sometimes a bruise will occur at the puncture site and rarely a blood clot or infection will occur in the vein. Certain individuals may feel light-headed during venipuncture.
Intravenous Access: Insertion of an intravenous catheter involves risk for hematoma at the site of the venous puncture. Very rarely, venous puncture can also result in a blood clot or infection
Rating Scales and Assessments: These are all noninvasive and should add no risk. The major disadvantages are the time taken to complete them, and possible breach of confidentiality.
Use of e-cigarette: Participants will be informed about the following Center for Disease Control (CDC) information about vaping: There have been recent reported cases of severe pulmonary illness linked to 'vaping' or e-cigarette use. These cases included symptoms such as coughing, shortness of breath, chest pain, fever, fatigue, nausea, vomiting, diarrhea, and/or abdominal pain. Some patients reported symptoms to have occurred over a few days and some reported to have occurred over a few weeks. Vaping-related disorders have ranged from mild to severe with hospitalization, intensive care with breathing machines and in some cases death. In most cases, but not all, people experiencing these symptoms were using cannabidiol (CBD) and marijuana (THC) e-liquids, and/or using e-cigarette devices and e-liquids that were mixed at home or purchased off market (such as purchasing an e-liquid or device on the street, not from a licensed retailer). Laboratory data show that Vitamin E Acetate, an additive in some THC-containing e-cigarette or vaping products is strongly linked to EVALI.

The Center for Disease Control (www.cdc.gov) has issued the following information on vaping:

- CDC and FDA recommend that people not use THC-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers.
- Vitamin E acetate should not be added to any e-cigarette, or vaping, products. Additionally, people should not add any other substances not intended by the manufacturer to products, including products purchased through retail establishments.
- Adults using nicotine-containing e-cigarette, or vaping, products as an alternative to cigarettes should not go back to smoking; they should weigh all available information and consider using FDA-approved smoking cessation medications. If they choose to use e-cigarettes as an alternative to cigarettes, they should completely switch from cigarettes to e-cigarettes and not partake in an extended period of dual use of both products that delays quitting smoking completely. They should contact their healthcare professional if they need help quitting tobacco products, including e-cigarettes, as well as if they have concerns about EVALI.
- E-cigarette, or vaping, products (nicotine- or THC-containing) should never be used by youths, young adults, or women who are pregnant.
- Adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products.
- THC use has been associated with a wide range of health effects, particularly with prolonged frequent use. The best way to avoid potentially harmful effects is to not use THC-containing e-cigarette, or vaping, products.
- Persons engaging in ongoing cannabis use that leads to significant impairment or distress should seek evidence-based treatment by a healthcare professional.

Use of propylene glycol/ vegetable glycerin: E-cigarettes contain other chemicals besides nicotine including propylene glycol/vegetable glycerin. At this time, we do not know the risks associated with the propylene glycol/ vegetable glycerin that may be in e-liquids used in this study. However, there may be unforeseen risks (such as allergic reactions). We will be using e-liquids with propylene glycol/vegetable

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glycerin concentrations that are available in e-liquids on the market. Some research has indicated that in large doses propylene glycol and vegetable glycerin can be harmful. Little is known about the short or long-term effects of inhaling flavorants. However, the participants will be allowed to stop the session at any point if they experience any side effect. Research staff will monitor e-cigarette use during the lab session. Participants who report recent THC vaping (within the last 90 days) will be monitored for EVALI symptoms, which are currently evaluated on our Health Assessment Checklist. Specifically, if a participant indicates EVALI symptoms (i.e. cough, shortness of breath, chest pain, nausea, vomiting, stomach pain, diarrhea, fever, chills, or weight loss), the researcher will assess if the symptom is related and proximal to a non-EVALI cause (e.g. Nausea/vomiting related to food poisoning, Shortness of breath related to seasonal allergies). If a reasonable & proximal cause is identified, participant will continue with session. If not, participation will be deemed ineligible (if identified at intake) or withdrawn (at lab sessions). We will consult with study pulmonologist for any cases in which the etiology of symptoms is not apparent or is unclear. Additionally, lung spirometry readings are already assessed intake. Participants who report THC vaping will receive education material about EVALI from https://www.yalemedicine.org/conditions/evali. All participants will have a physical exam(i.e. review of medical history, heart rate, blood pressure, lung spirometry, pulse oximetry) and be deemed healthy prior to participation and will continue to monitor their health closely during the study. Participants will be informed that if they experience any symptoms (cough, shortness of breath, chest pain, nausea, vomiting, stomach pain, diarrhea, fever, chills, or weight loss) or have other concerns, that they should let us know and also let their doctor know right away. Any participants reporting mild or moderate respiratory symptoms will be referred to their primary care physician or will be referred to care. They will be informed to the emergency room right away if their symptoms are severe increase rapidly. It is possible that the hospital may report cases of illness after using e-cigarettes to the State Health Department and the CDC. The report will contain the name and address of the person who is ill. Given the risk of THC vaping and EVALI, participants who report THC vaping and have endorsement of these symptoms at baseline without reasonable and proximal cause will be ineligible. If these participants develop symptoms during the study without reasonable and proximal cause, they will be withdrawn, referred to their primary care physician, or other care as needed.

Additionally, in rare cases there have been reports of e-cigarettes exploding and causing serious injury to people. Evidence suggests that these explosions are battery related. To avoid a vape related explosion the research staff has implemented the following Food and Drug Administration recommendations: 1) The research staff will keep loose batteries in a case to prevent contact with metal objects, 2) The research staff will always charge the battery with the charger that the e-cigarette came with 3) The e-cigarettes will not be charged overnight or left unattended 4) The research staff will replace the e-cigarette battery if it becomes wet or damaged. Furthermore, acute exposure to e-cigarette aerosol may result in mouth and throat irritation, dry cough at initial use and typical sensory effects of menthol in the mouth and throat.

Nicotine and flavor administration: Common side effects of nicotine include nausea, vomiting, heartburn, and elevated heart rate and blood pressure. Toxic doses of nicotine may cause abdominal pain, hypersalivation, diarrhea, dizziness, confusion, hearing and vision problems, syncope, seizures, hypotension, irregular pulse, and death. However, these toxic effects occur at doses 40 to 50 times higher than those that will be used in our studies. Moreover, by recruiting adults who already have experience with tobacco products, including e-cigs, we will further mitigate the risk of these side effects. Furthermore, our adult sample will be those who are regular users of combustible tobacco and the e-cigarette nicotine concentrations that will be used are in the range commonly used by both youth and adults. Nicotine intake during pregnancy may be associated with increased risk for spontaneous abortion, increased perinatal mortality and with low infant birth weights. We will exclude women who are pregnant or nursing from this study. Menthol administration produces typical sensory effects in the mouth and

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throat. The doses of menthol that are found in cough drops, ranging 1 to 10 mg are regarded to be safe. Despite ubiquitous use of menthol in a wide range of products, only few cases of menthol poisoning have been described in the literature following very high doses of menthol ingestion, 200 mg or more. Menthol poisoning reported to cause ataxia, confusion, coma, nausea, and vomiting. However, these toxic effects occur at doses 20 to 30 times that which will be used in our studies. We are not aware of any toxic effects from the tobacco flavor being used in this study, but participants will be told that if they feel any adverse events or want to stop they are free to do so. We will also monitor for adverse events.

Drug use: Participants will be asked about their current and past use of illicit "street" drugs at the intake to rule out substance abuse. If they are currently using drugs, they may not be eligible to participate. If at any time during their participation they report they want to hurt themselves or hurt anyone else, we will immediately direct them to appropriate authorities to ensure their safety.

Limits to confidentiality: All participants will be specifically told that we will not reveal any personal information collected as part of the research procedures, including their reported use of cigarettes, e-cigarettes and other substance use history. However, there is always the possibility that participation in this study may make others, such as friends and family members, aware of their tobacco use status. They will be told that if they do not feel comfortable with this, then they should not participate in the project. They will also be told that if they report any information to us about abuse or homicidal/suicidal behavior, we will be required to report this information to the appropriate authorities.

Lastly, any incidental clinical findings will be evaluated on a case by case basis and remain confidential unless there is concern about imminent danger. This will be clearly stipulated in the consent forms.

Smoking and Vaping and COVID-19: Although scientific evidence is incomplete, some studies have suggested that use of e-cigarettes may add to a persons risk of getting COVID -19 and may contribute to the severity of illness if you do get the virus. Additionally, smokers and e-cigarette users have to take their face masks off when they smoke or vape. So even between puffs, they may be unknowingly infected with the coronavirus, they might exhale contagious droplets and aerosols into the air, which could be inhaled by others nearby. Secondhand cigarette smoke is known to cause health problems, and although there isn't yet scientific proof that it can spread the coronavirus and cause COVID-19, it may be possible. Smoking or vaping inside is even riskier. In a closed environment, infectious droplets and particles can build up in the air, putting others in the room at risk if there's no ventilation.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

*Risks Associated with Blood Drawing – (*K01 Metabolism Study only)
To minimize risks associated with blood draws and IV-line insertion, experienced venipuncture-certified personnel will do all the blood-drawing procedures. Subjects will have approximately 60 ml of blood drawn at e-cigarette exposure lab session 1 and lab session 2. Therefore, the total amount of blood drawn during this study is 120 ml, which is well below the IRB guidelines of 450 ml within eight research weeks. We will advise participants to not donate blood for at least 4 weeks after participation.

Recruitment and Informed Consent
Recruitment will be through advertisements in Craigslist, Facebook, novelties (e.g. coasters, matchbooks, etc.) flyers in the community. At the initial intake session, potential participants will sign informed consent and complete initial assessments. Medical and substance abuse histories, urine drug and pregnancy tests, breath CO and urine cotinine levels will be obtained from all participants. If all the study criteria are met and consent is obtained, the research assistant will work with the participant to set up the experimental schedule.

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Protections against Risk

All the procedures will follow the guidelines provided by the National Advisory Council on Drug Abuse (NACDA) guidelines for administration of drugs for research purposes[71].

Specifically, the NACDA recognizes that substance abuse research involving adults is vital to understanding factors contributing to the initiation, maintenance and cessation of substance use. In order to reduce risk they have requested that all research requiring administration of drugs should include 1) A serious and concerted effort to link these individuals to drug abuse treatment, 2) Inclusion of medical screener to screen for any medical issues and if needed conduct a physical exam and 3) A thorough assessment of the risks entailed if participants are to be exposed to higher doses, rate of administration, and/or new route of administration than they would normally encounter by their own choice in their usual circumstance.

This study presents greater than minimal risk given that we will be providing participants with an electronic cigarette in a lab. However, we will reduce risk by:

- Obtaining consent from ≥21 year olds
- Requiring that adults report experience with e-cigs.
- Using well-defined inclusion/exclusion criteria to rule pre-existing medical conditions.
- Using study staff who have extensive expertise conducting tobacco research and working with adults and who are sensitive to the issues that may arise in working with combustible tobacco users.
- Monitor heart rate and blood pressure during experimental sessions
- Protect right to privacy through coding of data and proper storage of research records.
- Obtain a certificate of confidentiality from NIH to further protect the research records of these participants.
- Use the Yale TCORS Independent Data Safety Monitoring Board including experts in the field of tobacco use behaviors and challenge studies (Dr. Tony George, FRCPC, Professor and Co-Director, Division of Brain and Therapeutics, Dept. of Psychiatry, U of Toronto; Dr. Thomas Brandon, Professor and Chair, Department of Health Outcomes & Behavior, H. Lee Moffitt Cancer Center & Research Institute) and a statistical expert (Dr. Hanga Galfalvy, Assistant Professor of Neurobiology, Columbia University

COVID-19:

procedures: For the duration of the study, participants will be given a questionnaire daily to assess COVID symptoms they may be experiencing. This survey is in line with Yale's Return to Campus Protocol (https://ypps.yale.edu/sites/default/files/files/StayHome.pdf). If yes is endorsed for any symptom, the research team will follow up via phone call and ask participant to describe symptoms and rate symptom severity. For any symptoms described as severe and unrelated to other causes (i.e. headache for someone who is abstaining from their normal caffeine, muscle pain related to a workout, symptoms of seasonal allergies), the research team will evaluate the symptoms with a study physician. Based on physician recommendation, study participation will be paused until a negative COVID test can be produced. All participants will be instructed to contact their doctor and/or get a COVID test under these conditions. This COVID symptom check survey will be started the day prior to the first in person lab session. Participants will not be allowed to complete in person sessions unless the COVID symptom checks are completed. Once participant arrive at their appointment location, a COVID screening (including temperature and symptom check) will be conducted as part of their appointment. If a subject answers "yes" to any COVID screening question or has a temperature of ≥100˚F, their appointment must be discontinued and instructed to immediately contact their primary health care provider or call the Campus COVID Resource line (203-432-6604). For the safety of participants, to limit in-person interactions during experimental sessions, we will give instructions and communicate to

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participants from another location remotely using Zoom. Hand sanitizer will be available, and participants will be asked to wear gloves for the duration of the lab session. All devices and areas will be sanitized before and after each participant. Participants will be required to wear a mask over their nose and mouth when they are not vaping. This study will also recruit individuals that are fully vaccinated against COVID-19.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Greater than minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The Principal Investigator will be responsible for monitoring the safety and efficacy of this trial, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. The Yale TCORS has established a DSMB to provide the highest protection for study participants in all projects. The DSMB is composed of individuals not otherwise affiliated with the study but who are experienced in various aspects of conducting clinical trials and have expertise in tobacco research (Drs. Tony George (Chair), Thomas Brandon (Member) and Hanga Galfalvy [Statistician]). The Administrative Core will coordinate the DSMB meetings, will create formal summary reports, and will report DSMB comments back to the PI. The PI will provide the DSMB minutes to the Human Investigation Committee and to the NIH.The PI will also provide a summary of the DSM report to NIDA on an annual basis as part of the progress report. The DSM report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of adverse events (AEs) and Serious AEs, and any actions or changes with respect to the protocol. The DSM report to NIDA will also include, when available, the results of any efficacy data analysis conducted.

Data Monitoring Plan

Data will be collected using standardized forms and will be identified with the study ID of the participant. The codes that link the name of the participant and the study ID will be kept confidential by the Principal Investigator in a secured cabinet. A data manager will set up studies in the Oncore system and data will be scanned forms using the Teleforms software and exported to a database on a secure computer. Error checking and data validation will occur weekly and any problems will be queried and resolved immediately. Dr. Jackson will receive monthly data quality reports to check for completeness and accuracy of key demographic and prognostic variables, as well as rates of recruitment, retention, and follow-up. Preliminary analyses will be conducted to provide an overview of the data and test assumptions underlying the statistical entered using Teleforms data scanning. Furthermore, the data manager will perform data quality control functions, maintain the secure database on the Yale server, and interface with the statisticians and investigators.

Multiple measures are in place to ensure the validity and integrity of the data. First, all research staff receive Human Subjects Protection training. Second, formal training in clinical assessments and procedures will be conducted to ensure quality of the data and help implement and improve recruitment

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strategies so that enrollment goals are achieved. Third, weekly research staff meetings take place, as a forum for in-service training as well as to discuss questions regarding issues that arise in the research protocols. Lastly, adherence to assessment administration will be monitored and if research drift is observed, the research assistants will be re-trained.

Safety Monitoring Plan

During screening, participants will provide self-report of psychological and physical health. Participants will be terminated from participation if the investigator feels that their health or well-being may be threatened by continuation in the study. If a participant from the study shows interest in quitting use of any tobacco products, an appropriate referral will be made to one of our local smoking cessation programs.

This protocol presents a minor increase over minimal risk to the subjects and adverse events are not anticipated. In the unlikely event that such events occur, serious and unanticipated and related adverse events will be reported in writing within 48 hours to the Yale IRB and NIDA. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an SAE, the participant will be monitored by the investigator via ongoing status assessment until 1) a resolution is reached i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected 2) the SAE is determined to be clearly unrelated to the study intervention, or 3) the SAE results in death. Additionally, medical symptoms will be monitored throughout the study for any changes including symptoms associated with nicotine and EVALI (e.g., nausea, vomiting, rapid heartbeat, shortness of breath). All participants will be instructed to contact the PI and study staff about any side effects or changes in their health that they notice and these will be reviewed by a study physician (Dr. Steve Baldassari, a pulmonologist) as needed. Positive findings of a change in symptom to severe would trigger clinical review by PI and study physician with potential referral to a physician or ED if deemed potentially related to lung illness.

Outcome of SAEs will be periodically reported to NIDA. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

The principal investigator, Dr. Jackson, will be responsible for evaluating the adverse events and study data at regular intervals and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (at Risks to Subjects) or consent form (at Risks and Inconveniences) are required. During the review process, the PI will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Either the PI or the IRB or the DSMB have the authority to stop or suspend the study or require modifications. The review of all adverse events by the PI will determine the attribution and grade of severity of the adverse event by using the following scales**:**

Attribution of Risk Categories:

- Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
- Probable: Adverse event(s) will likely be related to investigational agent(s)
- Possible: Adverse event(s) may be related to investigational agent(s)
- Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
- Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Grades of Risk:

0: No adverse event or within normal limits
1: Mild adverse event
2: Moderate adverse event

3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4: Life-threatening or disabling adverse event
5: Fatal adverse event

d. For multi-site studies for which the Yale PI serves as the lead investigator:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
   ii. What provisions are in place for management of interim results? *Write here*
   iii. What will the multi-site process be for protocol modifications? *Write here*

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data Management: This pilot study outcomes will be collected using scannable forms (Teleforms) provided by the YCSTP Administrative Core. The scanned forms will be processed through the Teleforms software and exported to a database on a secure computer. Error checking and data validation will occur weekly and any problems will be queried and resolved immediately. The PI will receive monthly data quality reports to check for completeness and accuracy of key variables, as well as rates of recruitment, retention, and follow-up.

Statistical analyses for TCORS Menthol Pilot Study: Preliminary analyses will provide an overview of the data (e.g., randomization success, outcome distribution, missingness patterns). Outcome analyses will be intent-to-treat and using mixed-effects models. These models allow for different numbers of observations per subject, use all available data, and can handle missing-at-random data. If model assumptions will appear to be violated, we will transform the data or fit more flexible generalized linear or nonparametric mixed models. We will estimate effects for a larger study.

The mixed models will include gender (female, male) as a between-subject factor, flavor (menthol, tobacco), nicotine form (salt and freebase) as within-subject factors, and measurement time (time-within-experimental session). The models will also include all possible interactions among nicotine form and flavor and adjust for the stratification variables (sex). We anticipate significant main effects of flavor on liking/wanting of drug effects and e-cigarette taste. In addition, we expect significant main effects of nicotine form on irritation/harshness. Similar models will be used for secondary outcomes (nicotine-induced stimulation, craving and withdrawal).

Statistical Analysis for K01 Metabolism Study**:** Preliminary analyses will provide an overview of the data (e.g., randomization success, outcome distribution, missingness patterns). Outcome analyses will be intent-to-treat and using mixed-effects models. These models allow for different numbers of observations per subject, use all available data, and can handle missing-at-random data. If model assumptions appear to be violated, we will transform the data or fit more flexible generalized linear or nonparametric mixed models. Aim 1 and Aim 2: The mixed models will include baseline NMR (continuous), time within lab (within-subject factor), flavor (menthol, tobacco; within-subject factor), their three-way interaction, all corresponding two-way interactions and main effects. The model will also adjust for the between-subject factor sex (female, male). We will use Bayesian information criterion (BIC) to select the best fitting correlation structure for the repeated measures within subject. We will use graphical methods and polynomial terms to investigate whether the relationship between NMR and outcomes is linear. Statistical training and support will be provided by my co-mentor Dr. Gueorguieva who served as the Lead Biostatistician for Yale TCORS 1.0 and currently for Yale TCORS 2.0. She has also led statistical analysis efforts on similar experimental e-cig projects through the Yale TCORS[61]. **Power Analysis:** With 85

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subjects in total (43 women, 42 men) we will have 80% power at two-sided alpha level 0.05 to detect a correlation of 0.30 or bigger in absolute value between NMR and the primary study outcomes. For the within subject comparisons of the tobacco and menthol flavor sessions, with 85 individuals we will have 80% power at two-sided alpha level 0.05 to detect a medium effect size (Cohen's d'=0.32) for the primary study outcomes. This is a cross-over study, so all 85 participants will participate in Aim 1 and Aim 2 of this K01 proposal.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

B. DRUGS/BIOLOGICS ☐N/A (IND not applicable; ITP assessed)

TCORS Menthol Pilot Study

The Suorin iShare ™ and available e-liquids will be used for this study. The Suorin iShare ™ is a refillable pod system e-cigarette device composed of a battery without voltage control and a refillable pod that contains the e-liquid, mouthpiece and coil. It is among one of the pod e-cigarette devices that are used widely[57,58] .We have received an ITP from the FDA to use this e-cigarette device.

The following e-liquids will be purchased from e-liquid from American eLiquid Store:
1) DuraSmoke® Tobacco Menthol eLiquid 36mg/ml
2)Tobacco - Menthol eLiquid AmericaneLiquid® 36mg/ml
3)DuraSmoke® Tobacco Virginia eLiquid 36mg/ml
4)Tobacco - Virginia Flue Cured eLiquid AmericaneLiquid® 36mg/ml

We have received documentation from the American eLiquid Store stating that the above e-liquids were on the market prior to August 2016 so we do not need an ITP for these e-liquids.

K01 Metabolism Study

The JUUL ™ and JUULpods™[5%(59mg/ml)] will be used for this study. The JUUL™ is one of the most widely used pod e-cigarette devices[57,58] . We do not need an ITP from the FDA to use this e-cigarette device and products as they predate the enforcement compliance date.

The following JUULpods will be purchased:
1)Menthol eLiquid 59mg/ml (5%)nicotine

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2)VirginiaTobacco eLiquid 59mg/ml (5%)nicotine

1. If an exemption from IND filing requirements is sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*: IND not applicable.

2. Background Information: Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

TCORS Menthol Pilot Study

The devices and e-liquids used in this study are commercially available and we will obtain an ITP from the FDA. We obtain all our e-liquid from American eLiquid Store. The e-liquid mixture (propylene glycol [PG], vegetable glycerin [VG] and tobacco and menthol will consist of a concentrated flavor liquid added to a base liquid which will consist of a commonly used ration of 50% PG and 50% VG. PG is the original base liquid and is believed to produce a throat sensation ("throat hit") which mimics the feel of smoking a cigarette. VG is included to enhance the volume of vapor production, giving a greater sensory illusion of smoking. We will use 36mg/ml freebase nicotine and 36mg/ml nicotine salt e-liquid solutions. In order to ensure that we have adequate amount of e-liquid, of the same constituency, we will purchase large quantities of these solutions prior to starting these experiments which will be stored at and dispensed at John Pierce Labs. The commercially available Suorin iShare auto battery and Suorin iShare replacement pods will be used. This e-cigarette is similar in size and function to other commercially available more popular pod style devices. All of the e-liquids will be obtained from American eLiquid Store, which manufactures all its products in Wauwatosa, WI and reports being the first e-liquid manufacturer in the US to obtain the International Organization for Standardization (ISO) 9001:2008 and Current Good Manufacturing practices (cGMP) certification. A new e-cigarette device will be used for each subject, and new pods will be used for each experiment. Pods will be filled with e-liquid mixtures at John Pierce Labs.

K01 Metabolism Study

The commercially available JUUL ™ and commercially available JUULpods™[5%(59mg/ml)] will be used for this study. The JUULpods contain menthol flavor, tobacco flavor and 30% propylene glycol (PG) and 60% vegetable glycerin (VG). PG is the original base liquid and is believed to produce a throat sensation ("throat hit") which mimics the feel of smoking a cigarette. VG is included to enhance the volume of vapor production, giving a greater sensory illusion of smoking. A new e-cigarette device will be used for each subject, and new pods will be used for each experiment.

3. Source: Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☒YES ☐NO
If yes, by whom?

TCORS Menthol Pilot Study

The investigator will be purchasing the e-liquids from the American eLiquid Store website for this study. These will be stored at John Pierce Labs.

K01 Metabolism Study

The investigator will be purchasing the e-liquids from the JUUL company

4. Storage, Preparation and Use: Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

TCORS Menthol Pilot Study

After the e-liquids are received, they will be delivered and stored in appropriate light/temperature conditions at John Pierce Labs, which is a secured building. The liquids will be kept in a locked storage container in a drawer within the lab room. On the day prior to the lab sessions, a research assistant/associate/fellow who is not involved in the actual conduct of the lab sessions will fill the e-cigs. The information on randomizations to nicotine condition and flavors for each experimental session has been generated by study biostatisticians. This information is stored for each participant in an individual envelope and a printed study ID on the cover. These envelopes are stored at Pierce lab along with the purchased e-liquids. The individual filling the pods will be notified of which subject ID number needs to be filled and they will then go to Pierce labs and open the envelope and fill the three pods with the appropriate e-liquids. First, they will label each pod with the study ID number and lab 1 and 2 respectively. Each bottle of e-juice will be shaken vigorously prior to filling the pods. Next, they will open the top of the pod and using a mechanical pipette will load .9ml into the pipette from the e-juice bottle and carefully transfer it into the pod. This will be completed for all lab sessions. Each pod is then stored in a separate airtight bag to avoid cross contamination of flavors. The individual bags are then stored together in a larger bag labeled with the study ID number and stored back in the locked container until the lab is set to begin. Once the research assistant is ready to begin each lab, they will open the locked container, take the appropriate pod and leave the others. At the end of the lab, they will return the pod used that day to its proper bag and again return it to the lock box. None of the e-juice or pods will be transported outside of Pierce lab. The research staff will have the group randomization list and will dispense the appropriate e-liquid (nicotine condition, flavor) needed for each subject.

K01 Metabolism Study

After the pods and e-cigarettes are received, they will be delivered and stored in appropriate light/temperature conditions at YNHH pharmacy. On the day prior to the lab sessions, a pharmacist who is not involved in the actual conduct of the lab sessions will dispense the e-cigarette and pods. The information on randomizations to nicotine condition and flavors for each experimental session has been generated by study biostatisticians. This information is stored for each participant in an individual envelope and a printed study ID on the cover. These envelopes are stored at the pharmacy. The pharmacist will be notified of which subject ID number needs to be filled and they will open the envelope and dispense the e-cigarette with the appropriate pods. First, they will label each pod with the study ID number and lab 1 and 2 respectively. Each pod is then stored in a separate airtight bag to avoid cross contamination of flavors. The individual bags are then stored together in a larger bag labeled with the study ID number and stored back in the locked container until the lab is set to begin. Once the research assistant is ready to begin each lab, the pharmacist will have the pods and e-cigarette sent to the HRU. The research staff will have the group randomization list and will dispense the appropriate e-liquid flavor needed for each subject.

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Check applicable Investigational Drug Service utilized:

☒ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☒ Other: John Pierce Lab

Note: If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.

5. Use of Placebo: ☒Not applicable to this research project- "placebo" condition is absence of flavoring in the Nicotine?

B. DEVICES ☒N/A Tobacco distribution devices listed under biologics.

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol:

TCORS Menthol Pilot Study
We anticipate dropout so we will recruit 60 subjects. We anticipant 60 participants to participate in the initial appointment and 42 to complete lab session 1 and 37 to complete both lab sessions. Our target for completion is 30 participants.

K01 Metabolism Study
We anticipate dropout so each year (5 years total) we will recruit 23 subjects. We anticipant 23 participants to participate in the initial appointment and 17 to complete lab session 1 and 2. Our target for completion is 85 participants.

   b. If this is a multi-site study, give the total number of subjects targeted across all sites: *Write here*

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers ☒ Internet/web postings ☒ Radio
☒ Posters ☒ Mass email solicitation ☐ Telephone
☐ Letter ☐ Departmental/Center website ☐ Television
☐ Medical record review* ☐ Departmental/Center research boards ☒ Newspaper
☐ Departmental/Center newsletters ☐ Web-based clinical trial registries ☒ Clinicaltrails.gov
☒ YCCI Recruitment database ☒ Social Media (Twitter/Facebook):
☐ Other:

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

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a. Describe how potential subjects will be identified. Recruitment will be through advertisements at local colleges, in Craigslist, Facebook, YCCI Recruitment database Instagram, Twitter, Google ads and other social media platforms, radio ads, newspaper ads, novelties (e.g. coasters, matchbooks, etc.) flyers in the community(for example barbershops, hair salons, grocery stores in predominately Black communities) bus stops, within buses, word of mouth recruitment through community organizations, partnering with community groups, etc.

b. Describe how potential subjects are contacted. Potential participants can contact the study to determine eligibility through phone call, text message, or a website that will direct them to a Yale Qualtrics website where interested participants can complete a brief screening questionnaire- or may be referred from the TCORs screening protocol.

c.

d. Who is recruiting potential subjects? The PI and research staff will recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: *Write here*

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: We request a waiver of signed authorization only for initial participant recruitment/screening purposes to obtain interested participants' phone numbers and/or email for voice and text communication to make initial contact with the research team. At the first phone contact with the research team, participants will provide verbal consent for the screening process. If participants prefer to complete the online screener through the Yale Qualtrics system.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

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Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   After the screening process is complete and the participant is found to be eligible, the RA/PI will schedule them for an in-person (remote if necessary) intake. At the intake session, all eligible participants will be asked for written consent using the Yale HIC approved combined consent/HIPAA form. If the intake is done remotely, consent will be obtained via Redcap or mailed signed consent method for consenting will be used. The entire consent form will be reviewed in detail with the participant in a private, one-on-one setting at the first intake appointment. If remote, this will take place via phone or video conferencing (depending on technological capabilities of participant). All risks and potential benefits will be described. Any questions the participant may have will be addressed. If the participant wishes, they may take the consent form home and consider it further before signing. They may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the participant has signed the consent, they may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. All participants will receive a signed copy of the consent form to retain for their records.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   We will not be enrolling participants with limited decision-making capacity. We plan to exclude individuals with current serious psychiatric or medical illnesses. During the consenting process, the research assistant will read and review the consent form with the prospective participant. The research assistant will then ask the potential participant various questions about the consent form and study protocol to ensure the prospective participant sufficiently understands the study and the nature of their consent to participate.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

The information about participants' health that will be collected in this study includes:

- research study records (interviews, assessments, objective measures of smoking behavior, and self-reports).
- Medical and laboratory records of only those services provided in connection with this study (eg. lab tests)
- A video recording will be made of the e-cigarette use session. This recording will be labeled with an anonymous identifier and not their name.

We will collect names and demographic information. Identifiable information will be collected and used to enroll and contact participants. It will only be used for this purpose. This information will be stored in locked cabinet apart from the research records.

1. How will the research data be collected, recorded and stored?

   Research data will be collected using in-person interviews, assessments, objective measures of smoking behavior, and self-reports. All identifiable information (names and demographic information) will be stored in a locked file cabinet. All participants will be assigned a study participant ID made up of numbers and letters. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number (e.g., CM24). A list of IDs and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet. All other research data (interviews, assessments, objective measures of smoking behavior, and self-reports) will not contain identifiable information and will be labeled only with the subjects' unique numerical indicator.

2. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

3. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

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Several steps will be taken to safeguard the confidentiality of subjects and their data. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. All research data that is collected will be assigned a study participant number and that number will be the only link between participant names/identifying information and the digital databases. The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept in a locked file cabinet where it can only be accessed by senior level project staff. Any information published as a result of the study will be in aggregate and such that it will not permit identification of any participant. We are not directly assessing incidents of child abuse or elderly abuse. However, if this information is disclosed by a participant or volunteer in the context of this research, a report will be made to the Department of Child and Families Services or other agency as required by law. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document. All investigators and key personnel have taken the required Yale University HIPAA training. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. A list of numbers and the corresponding names will be maintained by the Principal Investigator in a locked research cabinet. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 and by additional protections of substance abuse treatment records afforded under Code of Federal Regulations (CFR) Part 2, Subpart E. All research personnel will be trained on human subjects' protection and HIPAA procedures.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

4. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. The data will be stored in a locked room for 7 years after the final data is collected. After this point, the Data Manager and Principal Investigator will oversee the process in which data is destroyed or de-identified.
5. If appropriate, has a Certificate of Confidentiality been obtained? A certificate will automatically be applied with the federal funding.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

TCORS Menthol Pilot Study

This study will provide preliminary data to the FDA to understand the reward/appeal of freebase vs. the salt form of nicotine when provided in pod e-cigarette devices to adult menthol smokers. This preliminary evidence may provide some clues about which form of nicotine (salt vs freebase) may be more acceptable to help adult menthol smokers transition to e-cigarettes for harm-reduction.

K01 Metabolism Study

There are no direct benefits to the participants. We expect that the results of the study will benefit science and address critical gaps in e-cigarette research by evaluating the impact of nicotine metabolism ratio on pharmacokinetics and subjective effects of menthol in e-cigarettes among African Americans who smoke. The outcomes of the project will provide the FDA with new information to

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further develop the knowledge base in understanding menthol flavor and its impact on nicotine dependence.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?
   This is not a treatment study and the alternative is to not participate.
2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   For TCORS Menthol Pilot
   We will compensate participants for time spent in this research project. Participants who complete the remote portion of the intake will be paid $30. Participants who complete the remote intake and the in-person portion will be paid an additional $20 (for a total of $50). For those who are ineligible after the remote intake will receive $30 via a gift card of their choosing (Amazon, Walmart, etc.).

   Participants (n=30) will receive $50 for each of the 3 experimental sessions. Participants will receive a $50 completion bonus after completing the third experimental session. For all appointments we will compensate participants $10/day for travel to appointments. Participants will receive a $30 gift card or cash for their 1 month follow up phone call. Each participant can earn up to $280 for appointments and an additional $40 for travel (total $320).

   We will validate parking in the Air Rights parking garage. We will provide round trip cab transportation to appointments if transportation is an issue and the $10 for travel will not be provided.

   For K01 Metabolism Study
   We will compensate participants for time spent in this research project. Participants will receive $30 for intake and assessments and $20 for biochemical measure collection. If ineligible after completing intake remotely participants will receive $30 compensation in the form of a gift card of their choosing (examples include but are not limited to Amazon, Wal-Mart, Target, Stop & Shop). All other payments will be in cash.

   Participants (n=85) will receive $200 each for the 2 experimental sessions. Participants will receive $50 for completing both lab sessions. We will compensate participants $10/day for travel to appointments. Each participant can earn up to $500 for appointments and an additional $30 for travel (total $530).

   We will validate parking in the Air Rights parking garage.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   There are no costs for participation.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? *Write here*

b. Where and from whom may treatment be obtained? *Write here*
c. Are there any limits to the treatment being provided? *Write here*
d. Who will pay for this treatment? *Write here*
e. How will the medical treatment be accessed by subjects? *Write here*

(a-e) If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises

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must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

1 Green, B, Dalton, P, Cowart, B, Shaffer, G, et al. (1996) 'Evaluating the "Labeled Magnitude Scale" for measuring sensations of taste and smell.' *Chemical Senses*, (3), pp. 323–34.

2 Soria, Rebeca, Stapleton, June M., Gilson, Stephen F., Sampson-Cone, Angela, et al. (1996) 'Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers'. *Psychopharmacology*, 128(3), pp. 221–226.

3 Lim, Juyun, Wood, Alison and Green, Barry G. (2009) 'Derivation and evaluation of a labeled hedonic scale'. *Chemical Senses*, 34(9), pp. 739–751.

4 United States Department of Health and Human Services (2014) 'The Health Consequences of Smoking—50 Years of Progress A Report of the Surgeon General'. *A Report of the Surgeon General*, p. 1081.

5 Giovino, Gary A, Villanti, Andrea C, Mowery, Paul D, Sevilimedu, Varadan, et al. (2015) 'Differential trends in cigarette smoking in the USA: is menthol slowing progress?' *Tobacco Control*, 24, pp. 28–37.

6 Foulds, Jonathan, Hooper, Monica Webb, Pletcher, Mark J. and Okuyemi, Kolawole S. (2010) 'Do smokers of menthol cigarettes find it harder to quit smoking?' *Nicotine and Tobacco Research*, 12, pp. S102-109.

7 Barna, Sandor, Rózsa, David, Varga, Jozsef, Fodor, Andrea, et al. (2018) 'First comparative results about the direct effect of traditional cigarette and e-cigarette smoking on lung alveolocapillary membrane using dynamic ventilation scintigraphy'. *Nuclear Medicine Communications*, p. 1. [online] Available from: http://insights.ovid.com/crossref?an=00006231-900000000-98464

8 Notley, Caitlin, Ward, Emma, Dawkins, Lynne and Holland, Richard (2018) 'The unique contribution of e-cigarettes for tobacco harm reduction in supporting smoking relapse prevention'. , pp. 1–12.

9 Benowitz, Neal L (2010) 'Nicotine addiction.' *The New England journal of medicine*, 362(24), pp. 2295–303. [online] Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2928221&tool=pmcentrez&rendertype=abstract (Accessed 20 June 2015)

10 Huang, Jidong, Duan, Zongshuan, Kwok, Julian, Binns, Steven, et al. (2019) 'Vaping vs. JUULing: How the Extraordinary Growth and Marketing of JUUL Transformed the US Retail E-cigarette Market'. *Tob Control*, 28(2), pp. 146–151.

11 Chen, L. (1976) 'pH of Smoke: A Review, Report Number N-170, Internal Document Of Lorillard Tobacco Company'. *Lorillard Tobacco Company*, p. 18.

12 Duell, Anna K., Pankow, James F. and Peyton, David H. (2018) 'Free-Base Nicotine Determination in Electronic Cigarette Liquids by1H NMR Spectroscopy'. *Chemical Research in Toxicology*.

13 Bowen, Adam and Xing, Chenyue (2015) 'Juule Labs Inc. US patent application US20150020824A1. Nicotine salt formulations for aerosol devices and methods thereof.'

14 O'Connell, Grant, Pritchard, John D., Prue, Chris, Thompson, Joseph, et al. (2019) 'A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers'. *Internal and Emergency Medicine*, (0123456789). [online] Available from: https://doi.org/10.1007/s11739-019-02025-3

APPROVED BY THE YALE UNIVERSITY IRB 8/3/2021

15 Audrain-McGovern, Janet, Strasser, Andrew A. and Wileyto, E. Paul (2016) 'The impact of flavoring on the rewarding and reinforcing value of e-cigarettes with nicotine among young adult smokers'. *Drug and Alcohol Dependence*, 166, pp. 263–267.
16 Harrell, M. B., Weaver, S. R., Loukas, A., Creamer, M., et al. (2017) 'Flavored e-cigarette use: Characterizing youth, young adult, and adult users'. *Preventive Medicine Reports*.
17 Kong, Grace, Morean, Meghan E., Cavallo, Dana A., Camenga, Deepa R. and Krishnan-Sarin, Suchitra (2015) 'Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults'. *Nicotine and Tobacco Research*, 17(7), pp. 847–854.
18 Rosbrook, Kathryn and Green, Barry G. (2016) 'Sensory effects of Menthol and Nicotine in an E-cigarette'. *Nicotine and Tobacco Research*, 18(7), pp. 1588–1595.
19 Garten, Samuel and Falkner, R. Victor (2003) 'Continual smoking of mentholated cigarettes may mask the early warning symptoms of respiratory disease'. *Preventive Medicine*, 37(4), pp. 291–296.
20 Galeotti, Nicoletta, Di Cesare Mannelli, Lorenzo, Mazzanti, Gabriela, Bartolini, Alessandro and Ghelardini, Carla (2002) 'Menthol: a natural analgesic compound'. *Neuroscience Letters*, 322(3), pp. 145–148.
21 Kim, Hyoshin, Lim, Juyun, Buehler, Stephanie S., Brinkman, Marielle C., et al. (2016) 'Role of sweet and other flavours in liking and disliking of electronic cigarettes'. *Tobacco Control*, 25, pp. ii55–ii61.
22 Webb Hooper, Monica and Smiley, Sabrina L (2018) 'Comparison of e-cigarette use among menthol and non- menthol smokers: findings from a Community Based sample'. *Ethnicity and Disease*, 28(3), pp. 153–160.
23 Siegel, Rebecca L, Miller, Kimberly D and Jemal, Ahmedin (2018) 'Cancer Statistics , 2018'. *CA Cancer J Clin*, 68, pp. 7–30.
24 Desantis, Carol E, Siegel, Rebecca L, Sauer, Ann Goding, Miller, Kimberly D, et al. (2016) 'Cancer Statistics for African Americans , 2016 : Progress and Opportunities in Reducing Racial Disparities'. *CA Cancer J Clin*, 66(4), pp. 290–308.
25 Haiman, Christopher A., Stram, Daniel O., Wilkens, Lynne R., Pike, Malcolmh C., et al. (2006) 'Ethnic and Racial Differences in the Smoking-Related Risk of Lung Cancer'. *The new england journal of Medicine*, 354(4), pp. 333–342.
26 Stram, Daniel O, Park, S Lani, Haiman, Christopher A, Murphy, Sharon E, et al. (2019) 'Racial / Ethnic Differences in Lung Cancer Incidence in the Multiethnic Cohort Study: An Update'. *JNCI J Natl Cancer Inst*, 111(8), pp. 811–819.
27 Okuyemi, Kolawole S, Harris, Kari Jo, Scheibmeir, Monica, Choi, Won S, et al. (2002) 'Light smokers : Issues and recommendations'. *Nicotine & Tobacco Research*, pp. S103–S112.
28 Benowitz, Neal L, Bernert, John T, Caraballo, Ralph S, Holiday, David B and Wang, Jiantong (2009) 'Optimal Serum Cotinine Levels for Distinguishing Cigarette Smokers and Nonsmokers Within Different Racial / Ethnic Groups in the United States Between 1999 and 2004'. *American Journal of Epidemiology*, 169(2), pp. 236–248.
29 Okuyemi, Kolawole S, Faseru, Babalola, Cox, Lisa Sanderson, Bronars, Carrie A and Ahluwalia, Jasjit S (2007) 'Relationship between menthol cigarettes and smoking cessation among African American light smokers'. *Addiction*, 102, pp. 1979–1986.
30 Pulvers, Kim, Romero, Devan R, Blanco, Lyzette, Sakuma, Kari-lyn K, et al. (2015) 'Light and Intermittent Smoking Among California Black , Hispanic / Latino , and Non-Hispanic White Men and Women'. *Nicotine & Tobacco Research*, 17(6), pp. 755–759.
31 Perez-Stable, Eliseo J., Herrera, Brenda, Jacob III, Peyton and Benowitz, Neal L. (1998) 'Nicotine Metabolism and Intake in Black and White Smokers'. *JAMA*, 280(2), pp. 152–156.
32 Hooper, Monica Webb, Zhao, Wei, Byrne, Margaret M., Davila, Evelyn, et al. (2011) 'Menthol cigarette smoking and health, Florida 2007 BRFSS'. *American Journal of Health Behavior*, 35(1), pp. 3–14.
33 Hatem, Samar, Attal, Nadine, Willer, Jean-Claude and Bouhassira, Didier (2006)

APPROVED BY THE YALE UNIVERSITY IRB 8/3/2021

'Psychophysical study of the effects of topical application of menthol in healthy volunteers'. *Pain*.
34 Wasner, Gunnar, Schattschneider, Jöm, Binder, Andreas and Baron, Ralf (2004) 'Topical menthol - A human model for cold pain by activation and sensitization of C nociceptors'. *Brain*.
35 Ha, Michael A, Smith, Gregory J, Cichocki, Joseph A, Fan, Lu, et al. (2015) 'Menthol Attenuates Respiratory Irritation and Elevates Blood Cotinine in Cigarette Smoke Exposed Mice'. *PLoS ONE*, 10(2), pp. 1–16.
36 Fagan, Pebbles, Moolchan, Eric T, Hart, Alton, Rose, Allison, et al. (2010) 'Nicotine dependence and quitting behaviors among menthol and non-menthol smokers with similar consumptive patterns'. *Addiction*, 105(Suppl 1), pp. 55–74.
37 Delnevo, Cristine D, Gundersen, Daniel A, Hrywna, Mary, Echeverria, Sandra E and Steinberg, Michael B (2011) 'Smoking-Cessation Prevalence Among U.S. Smokers of Menthol Versus Non-Menthol Cigarettes'. *Am J Prev Med*, 41(4), pp. 357–365. [online] Available from: http://dx.doi.org/10.1016/j.amepre.2011.06.039
38 Garten, Samuel and Falkner, R Victor (2004) 'Role of mentholated cigarettes in increased nicotine dependence and greater risk of tobacco-attributable disease'. *Preventive Medicine*, 38, pp. 793–798.
39 Delnevo, Cristine D, Ganz, Ollie and Goodwin, Renee D (2020) 'Banning Menthol Cigarettes : A Social Justice Issue Long Overdue'. *Nicotine and Tobacco Research*, pp. 1673–1675.
40 De Biasi, M and Dani, J A (2011) 'Reward, addiction, withdrawal to nicotine.' *Annual review of neuroscience*, 34, pp. 105–130. [online] Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3137256&tool=pmcentrez&rendertype=abstract
41 Alsharari, Shakir D., King, Justin R., Nordman, Jacob C., Muldoon, Pretal P., et al. (2015) 'Effects of menthol on nicotine pharmacokinetic, pharmacology and dependence in mice'. *PLoS ONE*, 10(9), pp. 1–16.
42 Kramlinger, Valerie M, Weymarn, Linda B Von and Murphy, Sharon E (2012) 'Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, β-nicotyrine and menthol'. *Chem Biol Interact*, 197, pp. 87–92.
43 Baurley, James W, Edlund, Christopher K, Pardamean, Carissa I, Conti, David V, et al. (2016) 'Genome-Wide Association of the Laboratory- Based Nicotine Metabolite Ratio in Three Ancestries'. *Nicotine & Tobacco Research*, pp. 1837–1844.
44 Shiffman, Saul, Dunbar, Michael S. and Benowitz, Neal L. (2014) 'A Comparison of Nicotine Biomarkers and Smoking Patterns in Daily and Non-daily Smokers'. *Cancer Epidemiology Biomarkers and Prevention*, 23(7), pp. 1264–1272.
45 Benowitz, Neal L, Perez-Stable, Eliseo J, Fong, Irving, Modin, Gunnard, et al. (1999) 'Ethnic Differences in N -Glucuronidation of Nicotine and Cotinine'. *Journal of Pharmacology and Experimental Therapeutics*, 291(3), pp. 1196–1203.
46 Smith, Philip H, Akpara, Ezinne, Haq, Raisa, El-miniawi, Mark and Thompson, Azure B. (2017) 'Gender and Menthol Cigarette Use in the United States: A Systematic Review of the Recent Literature (2011 – May 2017)'. *Current Addiction Reports*, 4(4), pp. 431–438.
47 Devito, Elise E and Krishnan-sarin, Suchitra (2018) 'E-cigarettes : Impact of E-liquid Components and Device Characteristics on Nicotine Exposure'. *Current Neuropharmacology*, 16(438–459), pp. 438–459.
48 Benowitz, N. L., Herrara, Brenda and III Peyton, Jacob (2004) 'Mentholated Cigarette Smoking Inhibits Nicotine Metabolism'. *Journal of Pharmacology and Experimental Therapeutics*, 310(3), pp. 1208–1215.
49 Fagan, Pebbles, Pokhrel, Pallav, Herzog, Thaddeus A, Pagano, Ian S, et al. (2016) 'Nicotine Metabolism in Young Adult Daily Menthol and Nonmenthol Smokers'. *Nicotine and Tobacco Research*, 18(4), pp. 437–446.
50 Fagan, Pebbles, Pohkrel, Pallav, Herzog, Thaddeus, Pagano, Ian, et al. (2015) 'Comparisons of three nicotine dependence scales in a multiethnic sample of young adult menthol and non-

APPROVED BY THE YALE UNIVERSITY IRB 8/3/2021

menthol smokers'. *Drug and Alcohol Dependence*, 149, pp. 203–211. [online] Available from: http://dx.doi.org/10.1016/j.drugalcdep.2015.02.005

51 Smiley, Sabrina L., DeAtley, Teresa, Rubin, Leslie F., Harvey, Emily, et al. (2018) 'Early Subjective Sensory Experiences with "Cigalike" E-cigarettes Among African American Menthol Smokers: A qualitative study'. *Nicotine and Tobacco Research*, 20(9), pp. 1069–1075.

52 Pulvers, Kim, Nollen, Nicole L, Rice, Myra, Schmid, Christopher H, et al. (2020) 'Effect of Pod e-Cigarettes vs Cigarettes on Carcinogen Exposure Among African American and Latinx Smokers A Randomized Clinical Trial'. *JAMA Network Open*, 3(11), pp. 1–13.

53 Hiler, Marzena, Breland, Alison, Spindle, Tory, Maloney, Sarah, et al. (2017) 'Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: Influence of liquid nicotine concentration and user experience'. *Experimental and Clinical Psychopharmacology*, 25(5), pp. 380–392.

54 Lopez, Alexa A., Hiler, Marzena, Maloney, Sarah, Eissenberg, Thomas and Breland, Alison B. (2016) 'Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers'. *Drug and Alcohol Dependence*, 169, pp. 33–40.

55 Pankow, James F, Kim, Kilsun, Mcwhirter, Kevin J, Luo, Wentai, et al. (2017) 'Benzene formation in electronic cigarettes'. *PLoS ONE*, 12(3), pp. 1–10.

56 Goniewicz, ML, Boykan, R and Messina, CR (2018) 'High exposure to nicotine among adolescents who use Juul and other vape pod systems (" pods ")'. *Tob Control*, 0(0), pp. 1–2.

57 Krishnan-Sarin, Suchitra, Jackson, Asti, Morean, Meghan, Kong, Grace, et al. (2019) 'E-cigarette devices used by high-school youth'. *Drug and Alcohol Dependence*, 194(October 2018), pp. 395–400. [online] Available from: https://linkinghub.elsevier.com/retrieve/pii/S0376871618308020

58 Barrington-Trimis, JL and Leventhal, Adam M. (2018) 'Adolescents ' Use of " Pod Mod " E-Cigarettes'. *The New England journal of medicine*, 379(12), pp. 1099–1102.

59 Lerman, Caryn, Tyndale, Rachel, Patterson, Freda, Wileyto, E Paul, et al. (2006) 'Nicotine metabolite ratio predicts efficacy of transdermal nicotine for smoking cessation'. *Clinical Pharmacology & Therapeutics*, 79(6), pp. 600–608.

60 Patterson, F, Schnoll, R A, Wileyto, E P, Pinto, A, et al. (2008) 'Toward Personalized Therapy for Smoking Cessation : A Randomized Placebo-controlled trial of Bupropion'. *Clinical Pharmacology & Therapeutics*, 84(3), pp. 320–325.

61 Krishnan-Sarin, Suchitra, Green, Barry G., Kong, Grace, Cavallo, Dana A., et al. (2017) 'Studying the interactive effects of menthol and nicotine among youth: An examination using e-cigarettes'. *Drug and Alcohol Dependence*, 180(August), pp. 193–199. [online] Available from: http://linkinghub.elsevier.com/retrieve/pii/S0376871617304337

62 St.Helen, Gideon, Dempsey, Delia A., Havel, Christopher M., Jacob, Peyton and Benowitz, Neal L. (2017) 'Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes'. *Drug and Alcohol Dependence*, 178, pp. 391–398.

63 St. Helen, Gideon, Havel, Christopher, Dempsey, Delia, Jacob III, Peyton and Benowitz, Neal L (2016) 'Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes'. *Addiction*, 111(3), pp. 535–544.

64 Shadel, William G., Edelen, Maria Orlando, Tucker, Joan S., Stucky, Brian D., et al. (2014) 'Development of the PROMIS nicotine dependence item banks'. *Nicotine and Tobacco Research*, 16(3), pp. s190–s201.

65 Morean, Meghan E, Krishnan-Sarin, Suchitra, Sussman, Steve, Foulds, Jonathan, et al. (2018) 'Psychometric Evaluation of the Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for Use With Electronic Cigarettes'. *Nicotine & Tobacco Research*, 00(00), pp. 1–9. [online] Available from: https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntx271/4782521

66 Nollen, Nicole L, Mayo, Matthew S, Cox, Lisa Sanderson, Benowitz, Neal L, et al. (2019) 'Factors That Explain Differences in Abstinence Between Black and White Smokers : A Prospective

Intervention Study'. *JNCI J Natl Cancer Inst*, 111(10), pp. 1–10.

67 Lewis-esquerre, Johanna M, Colby, Suzanne M, Leary, Tracy O, Eaton, Cheryl A, et al. (2005) 'Validation of the timeline follow-back in the assessment of adolescent smoking'. *Drug and Alcohol Dependence*, 79, pp. 33–43.

68 Toll, Benjamin A., Cooney, Ned L., McKee, Sherry A. and O'Malley, Stephanie S. (2006) 'Short communication Correspondence between Interactive Voice Response (IVR) and Timeline Followback (TLFB) reports of drinking behavior'. *Addictive Behaviors*, 31(4), pp. 726–731.

69 Helen, Gideon St., Benowitz, Neal L., Ahluwalia, Jasjit S., Tyndale, Rachel F, et al. (2019) 'Black Light Smokers: How Nicotine Intake and Carcinogen Exposure Differ Across Various Biobehavioral Factors'. *Journal of the National Medical Association*, pp. 1–12. [online] Available from: https://doi.org/10.1016/j.jnma.2019.04.004

70 Clausius, Rebecca L., Krebill, Ron, Mayo, Matthew S., Bronars, Carrie, et al. (2012) 'Evaluation of the Brief Questionnaire of Smoking Urges in Black Light Smokers'. *Nicotine & Tobacco Research*, 14(9), pp. 1110–1114.

71 NACDA (2006) 'Guidelines for Administration of Drugs to Human Subjects.'