HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: Effects of E-cigarette Flavors on Youth and Adults

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(*If applicable*) Clinicaltrials.gov Registration #: NCT03634839, NCT03635333

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.

Specific Aim 1: Examine the influence of cooling "icy" flavor components on the appeal, likelihood of use, and abuse potential of nicotine-containing e-cigs among young adults in two populations; (1) tobacco naïve young adults susceptible to e-cigarette use and (2) young adults who are current e-cigarette users. *In the first study, appeal and likelihood to use will be assessed among susceptible young adults after viewing advertising material for sweet-flavored e-cigarettes presented with and without a cooling "icy" component.* In the second study, participants will rate the flavor intensity, coolness, sweetness, and irritation (burning, stinging) experienced using the generalized Labeled Magnitude Scale (gLMS) and liking/disliking using the Labeled Hedonic Scale (LHS) following exposure to sweet-flavored nicotine containing e-cigarettes presented with and without a cooling "icy" component.

Primary Aim 1A (NOT COLLECTED IN THIS PROTOCOL): Examine e-cigarette appeal (liking) among youth who are susceptible to future use of e-cigarettes following exposure to advertising material (i.e. images) of sweet (fruit, dessert flavored) e-cigarettes with and without a cooling "icy" component. We hypothesize that susceptible youth will rate advertising materials with sweet and cooling flavor images as more appealing and greater likelihood to use than sweet flavors without a cooling flavor image.

Primary Aim 1B: Examine e-cig appeal and abuse liability (liking, craving and sensory responses in laboratory paradigm) among 18–20-year-old current regular e-cigarette users following exposure to nicotine salt containing fruit flavored e-cigarettes, with and without menthol) (e.g., Strawberry Chill & Strawberry). We will test both flavors in a single session. We hypothesize that inclusion of cooling flavors in a sweet e-cigarette will be positively associated with increases in e-cigarette liking and reinforcing efficacy as well as craving for sweet-flavored e-cigarettes and negatively associated with irritation and harshness.

Exploratory Aim: Explore if e-cigarette use (# days/past month; with/without nicotine) at a 1-month follow up is related to liking cooling flavors.

Specific Aim 2 (Study 2): Examine if flavors differentially influence reward from nicotine-containing e-cigs and e-cig use behaviors among younger and older adult combustible tobacco users. Participants will rate liking, nicotine withdrawal and stimulation using the Revised Drug Effects Questionnaire (DEQ) [2], flavor intensity, coolness, sweetness, and irritation (burning, stinging) experienced using the generalized Labeled Magnitude Scale (gLMS) [31,32,] and value using the Multiple Choice Questionnaire (MCQ; e-cig value) [3]

Primary Aim: Examine the influence of flavors (sweet, cool, tobacco) on reward (liking/wanting) from e-cigs containing one of two nicotine concentrations (6 mg/ml, 18 mg/ml; that vary in harshness), among younger and older adult combustible tobacco users following acute tobacco abstinence. We hypothesize that younger users will like/want sweet more than menthol or tobacco flavors, while older users will like/want tobacco flavors more than cool or sweet flavors. We also hypothesize that cool flavors, but not sweet flavors, will alter liking/wanting at the 18 mg/ml nicotine concentration, but not at 6 mg/ml nicotine.

Secondary Aim: Examine the influence of flavors on nicotine's effects on stimulation, harshness, and nicotine withdrawal and e-cig value; we expect that liking/wanting for cool flavors, but not sweet or tobacco flavors, will be positively associated with nicotine-induced stimulation and withdrawal-alleviation, but negatively associated with nicotine harshness.

Exploratory Aim [ON HOLD]: Explore flavor choice during a two-week ad-libitum e-cig use period. We expect that younger smokers will use more sweet flavored e-cigs while older smokers will use more tobacco flavored e-cigs. We will also explore nicotine-dose related differences in the use of sweet, cool and tobacco flavors by younger and older smokers.

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Specific Aim 3 (Study 1 & 2): Examine the feasibility and accuracy of a wearable smartband to detect e-cigarette puffing behavior. While in the lab for the e-cigarette use sessions, we will have participants wear a small smartband on their wrist, on the same hand they use to vape the e-cigarette. They will put on the smartband prior to starting the vaping session. The silicone smartband is small and lightweight, like a smartwatch or fitbit. The smartband collects movement data from geospatial sensors as the participant moves their arm and hand. The sensor data will be used to measure the movement during the directed e-cigarette puffing during the lab session. There are no changes to the lab procedure or puffing instructions.

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

	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Study 1 1 exp. sessions + 1 mos. follow up				10 completers	30 completers Analyze results Present at annual TCORS meeting
Study 2 3 exp. sessions + 2 week ad-lib use period	10 completers	20 completers	40 completers	40 completers	10 completers Analyze results Present at annual TCORS meeting

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.
   Most US tobacco products contain a wide variety of flavorants, with an estimated 7000+ flavors in e-cigarettes (e-cigs) alone. Flavors may enhance the appeal of tobacco products by their positive attributes (e.g. aroma/taste of sweet flavors) and/or by their ability to ameliorate nicotine/tobacco harshness (e.g. cool flavors)[1-4]. For example, our recent evidence suggests that the cool flavor, menthol, improved the taste of inhaled nicotine[4], reduced irritation from inhaled nicotine[2] and enhanced reward from high, but not low, doses of inhaled nicotine [4], among young e-cig users. Furthermore, these flavor attributes could differentially impact use behaviors and addiction among youth who are experimenting with tobacco products relative to more established users, and among those who may be looking to switch to potentially harm-reducing products like e-cigs. Understanding the impact of these fundamental flavor attributes on use and addiction to tobacco/nicotine is critical to develop and support regulations of flavors in tobacco products. The overarching aim of this proposal is to examine the influence of different flavor attributes of popular sweet and cooling flavors on the abuse potential and use of e-cigs among susceptible youth and adult combustible tobacco users.

   While the Family Tobacco Prevention and Tobacco Control Act (FSPTCA) banned the sale of cigarettes with added artificial and natural flavors in 2009, menthol is still allowed in cigarettes. Even the new FSPTCA regulations (introduced in May 2016) do not address menthol in cigarettes or the inclusion of any of the other assortments of flavors or sweeteners in any of the other tobacco products (e.g., cigars/cigarillos, hookah, e-cigs). One potential reason for the limited action on flavors is the limited scientific evidence on the influence on flavors and sweeteners on nicotine's

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abuse potential. To support the regulation of tobacco products, the FDA requires rigorous scientific information on which to base their rulings and support these rulings in legal challenges. These regulatory decisions are further complicated by the multitude of flavors available in tobacco products and the constant innovation by the tobacco industry to use flavorant chemicals to enhance and maintain appeal for these products.

To understand if and how flavors increase the appeal of tobacco products, it is necessary to understand the sensory basis and perceptual attributes of flavors and tobacco. The senses of smell (olfaction), taste, temperature and chemesthesis all play central roles in the flavor of tobacco products[4] Interestingly, menthol, one of the most commonly used tobacco product flavorants [6,7], is thought to enhance palatability of nicotine but is in itself also a chemesthetic stimulus which evokes cooling [8-11] and burning/stinging sensations at moderate to high concentrations [3].
Interestingly, menthol, one of the most commonly used tobacco product flavorants [5,6], is thought to enhance palatability of nicotine but is in itself also a chemesthetic stimulus which evokes cooling [7-10] and burning/stinging sensations at moderate to high concentrations [11].

Flavored tobacco products are very popular among youth [12-16]. In the US, 80% of youth and 73% of young adult tobacco users currently use flavored tobacco products [13]. We have shown that flavors are also one of the main reasons reported by youth for using e-cigs and cigars [17,18]. However, despite the above epidemiological evidence, there is no data supporting a causal link between the appeal of flavors and initiation of use of tobacco products. Flavored tobacco products are also used by adult tobacco users, but they appear to be more popular among younger than older adult users. For instance, use of flavored cigarettes decreases with age (11.9% among 17-26 yr.-old and 6.7% among >26 yr.-old smokers[19]) and while 42.9% of adult cigar users reported using flavored cigars, this rate was greater among younger adults [15]. Our evidence suggests that use of flavors is related to greater intensity of e-cig use among youth but not among adults. Further, a recent review of general flavor preferences [20] observed that children and adolescents had higher preferences for sweet tastes and odors when compared with adults, and that bitter and irritant responses become muted with increasing age. This raises the question of whether flavors in tobacco products are important and necessary for older tobacco users, who may have reduced chemesthesis sensations from nicotine/tobacco, may be more nicotine dependent, and may use tobacco primarily for the nicotine.

In addition, variation in taste perception and nicotine aversiveness is a well-known phenomenon in humans and may be due to sequence variations in genes coding for taste and nicotinic acetylcholine receptors[51-54]. Thus, to further understand the impact of genetic variation on taste perception and nicotine aversiveness in regard to flavored tobacco products, we will analyze variations in genes that code for bitter and sweet taste receptors (Tas2R38, Tas1R1, Tas2R7)[55, 56], and the CHRNA5 gene which is associated with nicotine aversiveness and encodes for a nicotinic receptor subunit[54].

Another crucial unresolved issue is whether the availability of flavors in potentially harm-reducing tobacco/nicotine products are essential to motivate and support the switch from combustible tobacco products. For example, as highlighted earlier, e-cigs are being proposed as a harm-reduction strategy for combustible tobacco users. Therefore, regulatory efforts on e-cigarettes need to strike a balance between reducing their appeal to youth at risk of progressing to regular use of combustible products and enhancing their appeal to combustible tobacco users seeking to quit combustible product use. While flavors and nicotine levels in e-cigs have been identified as features that are important to adult cigarette smokers [21-23], there has been limited information on the types of flavors that are important to support switching for harm-reduction. At least one initial survey study suggests that most adult smokers seemed to prefer e-cigs that tasted like a cigarette [24]. In contrast, secondary analyses of evidence from a clinical trial that switched smokers to snus or nicotine gum, reported that most participants chose to use cool (minty) or fruit flavored products [25].

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Study 1 will use established methodology and sensory experiments to examine the influence of sweet and cooling flavors, and combinations thereof, on the appeal and abuse potential of e-cigs containing a common nicotine concentrations among young adults with established e-cigarette use. This study will also explore if sensory responses to flavors predict emergence in e-cigarette and other tobacco use behaviors at one-month follow ups. Additionally, this study will also include a component examining liking among susceptible young adults after viewing e-cigarette containing images with sweet and cooling flvaors.
Study 2 will use established experimental methods to examine if different classes of flavors (i.e., sweet, cool, tobacco), when combined with nicotine concentrations differing in harshness (6 and 18 mg/ml) alter appeal and nicotine reward among younger and older combustible tobacco users. Importantly, this study will also explore the differential influence of sweet, cool, and tobacco flavors on switching from combustible tobacco product use to e-cigarettes, among younger and older adult combustible tobacco users. The evidence generated from this novel proposal is crucial to support regulations directed at flavors in tobacco/nicotine products like e-cigs, which will likely need to strike a balance between reducing the appeal of these products for youth and enhancing their appeal for combustible tobacco users looking to switch to use of e-cigs for harm-reduction.

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.
We propose 2 double-blind, placebo-controlled studies.

Study 1B: Examine the influence of sweet and cooling flavors on the appeal and abuse potential of nicotine-containing e-cigs among susceptible young adults. Forty young adults (18-20 years of age) who have with e-cig use (used at least 10x in lifetime and at least once in the past 30-days) , will participate in 1 laboratory session, and receive all the exposures in table below.

	Sweet (Watermelon)	
	Non-menthol	Menthol
36 mg/ml nicotine salt	S_1-S_{40}	S_1-S_{40}

During the session participants will be exposed, in random order, to sweet (watermelon e-liquid) with and without menthol, in a 36mg/ml nicotine salt, as nicotine salt is currently the most common and popular nicotine formulation among young adult e-cigarette users. Each of the two exposures will consist of a single fixed-puff bout (10 puffs; each 3-sec duration, with a 30-sec inter-puff interval). These procedures were adapted from our recent work [26] where we used three puff bouts to achieve sufficient and sustained increases in nicotine levels, to conduct an adequate test of nicotine exposure on outcomes of interest. As we are not examining withdrawal and craving, a single puff bout should be sufficient to capture this. Each exposure will be separated 30 minutes to allow flavor sensation to dissipate as well as give time for nicotine effects to reduce. Prior to testing, subjects will be familiarized with the sensory and hedonic rating scales.[27-31] Cotinine and CO levels will be used to confirm nicotine/tobacco non-use status. After each exposure, participants will rate the flavor intensity, coolness, sweetness, and irritation (burning, stinging) experienced using the generalized Labeled Magnitude Scale (gLMS) [31,32], and liking/disliking of the flavor sensation using the Labeled Hedonic Scale (LHS)[27]. These procedures are adapted from our earlier work [2]. Follow ups: Participants will be contacted at 1-month time-points to determine changes in use of e-cigs (with and without nicotine), any health changes, and other tobacco use (number of days used/30 days) using Timeline Follow-Back methods[33-37]. We will examine whether the sensory attributes of

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different flavors observed in the experimental session predicts use of nicotine-containing e-cigs, or preference for flavors, during the follow-up periods.

For the 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 (e.g. 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.

During the lab session, we will have participants wear a small smartband on their wrist, on the same hand they use to vape the e-cigarette. The smartband collects movement data from geospatial sensors as the participant moves their arm and hand. The sensor data will be used to measure the movement during the directed e-cigarette puffing during the lab session. There are no changes to the lab procedure or puffing instructions.

Once the participant arrives 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 and instructed to immediately contact their primary health care provide or call the Campus COVID Resource line (203-432-6604).

Study 2: Examine if flavors differentially influence reward from nicotine-containing e-cigs and e-cig use behaviors among younger and older adult combustible tobacco users. 120 cigarette smokers (60 young adult users; 60 older adult users) will be randomized into one of two nicotine-concentration groups (6 or 18 mg/ml); Sex (male, female) and use of mentholated tobacco products (yes, no) will be stratifying factors. Within each nicotine condition (6 or 18 mg/ml), participants will receive, in counterbalanced order, each of four flavors (tobacco, menthol, cherry and vanilla) during four different laboratory sessions separated by at least 24 hrs.

Nicotine	Flavors (Within Ss Factor)			
(Between Ss Factor)	Tobacco	Menthol	Vanilla	Cherry
6 mg/ml	S_1-S_{60}	S_1-S_{60}	S_1-S_{60}	S_1-S_{60}
18 mg/ml	S_{70}-S_{120}	S_{70}-S_{120}	S_{70}-S_{120}	S_{70}-S_{120}

	Puff Bouts					
Set up and baseline assessments	10 Puffs	Break	10 Puffs	Break	10 Puffs	**End of lab assessments**
15 mins	5min	10 min	5min	10 min	5min	15 minutes

Participants will be required to be abstinent from cigarettes for 12 hrs. (CO level <9 ppm) prior to each session, which will consist of 3 fixed-puffing bouts (10 puffs; each 3-sec duration, with a 30-sec inter-puff interval); each fixed-puff bout will be separated by 10 min (see Table above). These

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procedures were adapted from our recent work [26] where we used three puff bouts to achieve sufficient and sustained increases in nicotine levels, to conduct an adequate test of nicotine exposure on outcomes of interest. Per our current practice, we will record timed instructions for each puffing bout and participants will be trained to follow these directions. Nicotine/cotinine levels will be monitored using saliva samples obtained at baseline and then at the end of each puff bout. Prior to testing, participants will be familiarized with the assessments and trained in how to puff e-cigs. Training will be conducted using e-cigs that contain the base liquid of 50% propylene glycol/50% vegetable glycerin.

The Revised Drug Effects Questionnaire (DEQ; e-cig liking/wanting, nicotine withdrawal, and stimulation) [2], Multiple Choice Questionnaire (MCQ; e-cig value) [3] will be assessed after each 10-puff exposure period (see below for the list of assessments).

During the lab session, we will have participants wear a small smartband on their wrist, on the same hand they use to vape the e-cigarette. The smartband collects movement data from geospatial sensors as the participant moves their arm and hand. The sensor data will be used to measure the movement during the directed e-cigarette puffing during the lab session. There are no changes to the lab procedure or puffing instructions.

[ON HOLD – Exploratory Outcome] Immediately after the last session is completed, participants will start a 2-week ad-libitum e-cig use period. During this period, we will provide participants with the 3 e-cigs that they tried during the laboratory sessions (containing the nicotine level they were assigned to [6 or 18 mg/ml] in combination with each of the three flavors (tobacco, menthol, strawberry/vanilla). We will provide participants with new pods on a weekly basis (or more frequently if needed depending on use patterns) and collect the used ones. Once weekly, subjects will return for an appointment to receive new e-cigarette pods filled with e-liquid and we will collect the used pods. During appointments held at our clinic, we will ask subjects about their e-cigarettes and cigarette use, how they are feeling, and we will collect CO levels, blood pressure and heart rate, and a measure of how well the subject's lungs work by measuring how much air they exhale and how quickly. We well also collect pulse oximetry, which measures how well oxygen is being sent through the body. This appointment should only take approximately 30 minutes to complete. Participants will be told to only use the e-cigs provided and not smoke combustible tobacco products or use other non-study-related tobacco products during this period. We will emphasize the importance of not sharing their e-cigs with others, or mixing e-liquids, and provide individuals with a single disposable mouthpiece for each pod. The pods will be weighed and labeled before they are given to the participants and will be weighed again when they are returned to determine how much e-liquid was used from each. The outcome will be the amount of e-liquid of each flavor (tobacco, menthol, strawberry/vanilla) that was used during this 2-wk period.

We will also ask subjects to fill out a short online questionnaire remotely every day assessing their craving and feelings regarding not using cigarettes.

Abstinence from combustible tobacco products will be reinforced using monetary incentives for daily negative CO levels < 9 ppm. We have extensive experience using incentives to support cigarette abstinence among youth [27,28] and have also successfully used these procedures to ensure 100% cigarette abstinence among adult smokers prior to PET neuroimaging and other experiments[29-31]. More recently we have successfully adapted these procedures for use via mobile phones among treatment-seeking adolescent smokers (n=15) and observed that 60% of the participants had biochemically verified abstinence following four weeks of mobile-phone CM implementation[32]. We expect higher rates in the proposed study because participants will have access to nicotine containing e-cigs as an alternative to cigarettes. For the current study, we will assess and provide daily incentives for cigarette abstinence assessed using CO < 9 ppm. CO levels will be obtained during appointments held in our clinic once weekly or during online appointments. For online

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appointments, participants will be given a microCO monitor to take home with them and will learn to use their mobile phones to video record themselves showing the CO monitor being reset, exhaling into the CO monitor, and the final reading on the display. All video clips will have a date and a timestamp and participants will upload it directly to the secure study website from their phones. We will text participants at random times and they will have the option of either taking and transmitting a video of themselves providing a CO level, or communicating with us via Facetime or Skype. If participants do not have a cell phone, we can loan them a cell phone for the duration of the study. Participants will be paid daily ($5) for negative CO levels and completion of online questionnaires ($5); payments will be withheld for positive CO levels. They will also receive incentives for coming into our clinic every other day (or daily if needed) to receive refills on their e-liquids, at which time we will also weigh all their e-cig pods and document how much has been used. Thus, through use of monetary incentives we will ensure combustible tobacco abstinence and use of e-cigs.

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).

Participants will be contacted at 1 month and 6 months to determine if they continued to use e-cigs (with and without nicotine) and other tobacco (# days used/30 days) using Timeline Follow-Back methods[33-36].

a) Assessments

1. General Labeled Magnitude Scale (gLMS) [32] (Study 1, Study 2): In Study 1 gLMS ratings will be obtained following each puff exposure and in Study 2 following each 10-puff bout**.** Participants will rate overall intensity, sweetness, coolness, irritation 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[37]. 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.
2. Labeled Hedonic Scale (LHS)[38] (Study 1, Study 2): Liking will be assessed 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",

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"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.

3. E-cig Effects (Adapted from Drug Effects Questionnaire (DEQ)[26] (Study 1, Study 2): A modified version of the Drug Effects Questionnaire [2,39] 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." Following each 10-puff bout, we will assess E-cig Liking/Wanting (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"). At baseline and following each fixed-dose bout, we will also assess 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").
4. Multiple Choice Questionnaire to assess e-cig value (Adapted from Multiple Choice Procedure (MCP)[3,26] (Study 1, Study 2): At the end of each fixed-10-puff period, participants will be asked to make discrete hypothetical choices between 10-puffs of the e-cig they had just used or a series of 44 monetary values ($0.25-$15.06). The minimum monetary value at which money is chosen over the e-cig puffs is a contingency-based estimate of e-cig value. At the end of each lab session, participants will be given a choice between another 10 e-cig puffs or one of the monetary amounts they picked in the MCPs completed earlier.
5. Asthma Control Test[40] (Study 1, Study 2): At intake, at every in-person visit, and at follow up appointments, 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
6. Fatigue[41] (Study 1, Study 2): At intake, at every in-person visit, and at follow up appointments, we will use the 7-item PROMIS measure of fatigue which rates fatigue from 1=" never" to 5=" always".
7. Shortness of Breath (Study 1, Study 2): At intake, at every in-person visit, and at follow up appointments, 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.
8. Carbon Monoxide (CO) levels (Study 1, Study 2): CO levels in exhaled breath will be measured using a MicroCO breath CO monitor and levels of < 6 ppm will be used to ensure abstinence prior to the lab sessions, *during the 2-week ad-libitum use period [ad lib portion ON HOLD*] (Study 2), and at the follow-ups (Study 1).
9. Urine Cotinine levels (Study 1, Study 2): Cotinine levels are accurate indicators of tobacco use even among adolescents[42,43] Urine samples will be obtained at intake to verify eligibility for Study 1 and 2 and prior to the start of each laboratory session. *We will also assess cotinine levels once a week during the ad-lib session of Study 2 [ad lib portion ON HOLD]*. Cotinine levels will be determined using LC/MS by the YCSTP core laboratory.
10. Salivary Nicotine and Cotinine levels (Study 1, Study 2): In Study 1, salivary samples for nicotine and Cotinine levels will be obtained at baseline, at the end of each exposure, and then again at the beginning of each exposure (10 samples). In Study 2, saliva samples will be obtained at baseline, and following each 10-puff bout (4 samples). In addition, cotinine levels will be assessed during each week during the ad-lib period. 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.
11. Heart Rate, Blood Pressure, Pulse Oximetry, Pregnancy Test, Spirometry (Study 1, Study 2): These measures will be assessed to monitor health status at baseline and throughout the study at each in-person visit. Heart rate, spirometry, and blood pressure will be assessed. Pulse oximetry is the measurement of the oxygen in the blood. We will administer pregnancy tests to all female participants at baseline and every lab visit.

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12. Health assessment checklist (Study 1, Study 2): 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 and at follow up appointments.
13. Qualitative Interview (Study 1): At the end of sessions, all participants will answer qualtitaitve questions comparing the experience between the e-liquids sampled.
14. Exit interview (Study 2): All participants will receive an exit interview to assess their subjective experiences with the e-cigarettes at the end of the ad-lib period.
15. COVID Symptom Checklist (Study 1, Study 2): We will monitor COVID symptoms daily. Participants with symptoms deemed potentially related to COVID will not be allowed for in-person visits.

Additional Assessments to be Completed at Intake and Follow-up:

- Demographic Information (Study 1, Study 2: At Intake; updated at follow up): Age, race, marital status, educational and occupational levels and medical history will be assessed with interviews and self-report forms.
- PROMIS Physical Function Short Form 4a (Study 1, Study 2: At intake): Physical functioning will be assessed as part of the medical history using the following four items: (1) Are you able to do chores such as vacuuming or yard work?, (2) Are you able to go for a walk of at least 15 minutes?, (3) Are you able to run errands and shop?, (4) Are you able to go up and down stairs at a normal pace? Response options for these questions are “Without any difficulty”, “With a little difficulty”, “With some difficulty”, “With much difficulty” and “Unable to do so”.
- Nicotine Dependence (Study 1: At Intake & Follow up; Study 2: At Intake; Post two-week ad-lib period): We will use the 8-item PROMIS measure of nicotine dependence developed for cigarettes [44] and which we have validated for e-cigs[45], which shows internal consistency & measurement invariance across sex and race.
- Tobacco Use History Questionnaire (Study 1, 2: At Intake, updated at Follow-up): Self-reports will be obtained from all participants; questions will be benchmarked to the NIDA PATH data.
- Timeline Follow Back Interview [35,36] (Study 1 Intake, Follow Up, Study 2: At Intake, Laboratory Period, Ad-Lib Period and Follow Up): Use of cigarettes and e-cigs (with or without nicotine) will be examined using a 30-day TLFB at intake, laboratory sessions, ad-lib period, and follow-ups. Test-retest reliability is high in adult smokers, and we have used it with younger smokers[46] and those with e-cigarette experience.
- Minnesota Nicotine Withdrawal Questionnaire, Questionnaire of Smoking Urges (Study 2: At Intake, Laboratory Period, Ad-Lib Period and Follow Up)[47,48]: Change in nicotine withdrawal and smoking urges over the course of the study will be assessed using the Minnesota Nicotine Withdrawal Questionnaire and the Questionnaire of Smoking Urges, which have been well-validated in cigarette smokers.
- Exit Interview (Study 2, Final Outpatient Interview, ON HOLD): An exit interview will be administered to participants at the end of their outpatient period. This will qualitatively explore their thoughts on the cigarette sample, how it is similar or dissimilar to cigarettes and what they liked and disliked about the vaping experience.

5. Genetic Testing N/A ☐

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned We plan to use the samples to conduct pharmacogenomics studies related to the targeted neurochemical systems. For example, since we are investigating the effect of e-liquid flavors on the appeal of e-cigarettes in adult established smokers (study 2), we will explore the role of various genetic markers relating to bitter and sweet taste receptors and nicotine aversion in these subjects. The samples may also be stored for future research to examine other

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genes related to tobacco product use. For this we may look through genetic markers throughout the participant's genomes to identify one or more markers near, or within genes, influencing risk of tobacco product use. We will decode all or part of the sequence of their DNA. We may also study genes that influence other behaviors and characteristics that may be related to tobacco product use such as alcohol drinking or impulsivity. We may also study other substances in the blood to help us learn more about genetic variation, gene effects, characteristics, and different population groups. The DNA will also be used to study differences in genes and sequences between individuals. Results from these genetic studies will be shared with public databases (per our data sharing agreement with NIH) but no personal identifying information will be shared.

ii. the plan for the collection of material or the conditions under which material will be received
The genetics saliva samples will be collected at the time of physical exam from those who have consented to providing these samples. The samples will be stored in a -20-degree Celsius freezer prior to being de-identified and transported to Dr. Gelernter's lab.

i. the types of information about the donor/individual contributors that will be entered into a database The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab.

ii. the methods to uphold confidentiality Identifiers will be stored in a locked file cabinet at the PI's Office

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? Genetic testing will only be conducted for research purposes and the results will be available to investigators on this study. Eventually, DNA extracted may be available to any qualified researcher; so, will some of the genetic information from the DNA.

C. Is widespread sharing of materials planned? Yes

D. When and under what conditions will materials be stripped of all identifiers? The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab. All samples are made anonymous prior to distribution. Some of the investigators may have commercial interests.

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? Donors will be told during the consenting process that they can choose to withdraw their materials at any time

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? Donors will be told to contact the PI directly to request withdrawal of participation

F. Describe the provisions for protection of participant privacy The PI will retain identifiable information about each sample that is collected. The samples identified by code and stripped of any identifiers prior to being transported to Dr. Gelernter's lab

G. Describe the methods for the security of storage and sharing of materials the identifiers will be stored in a locked file cabinet at the PI's office.

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.
160 healthy participants (50% female) will be recruited.
Study 1: 40 participants will be 18-20, have used e-cigs at least 10 times (with use reported in the past 30-days)
Study 2: 120 participants will be 21-50 years of age; Adult daily smokers with a least some e-cigarette experience (at least 10 uses in the past six months, less than weekly use currently, no strong flavor/device preferences) not currently seeking to quit smoking.

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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
☐Non-English Speaking persons	☐ Prisoners	☐Economically disadvantaged
☐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?

Study 1:
Inclusion Criteria:
(1) Ages 18-20
(2) Able to read and write
(3) Have used e-cigs at least 10 times in lifetime
(4) Have used flavored e-cigs
(5) Have used e-cigs in the past 30 days
(6) Cotinine level >200 ng/ml (indicating recent cotinine use)

Exclusion Criteria:
(1) Current criteria for moderate or severe cannabis and alcohol use disorder as per DSM-V criteria.
(2) Current criteria for mild, moderate or severe substance use disorder on any other psychoactive substances as per DSM-V criteria except for tobacco use disorder
(3) Use of psychoactive drugs including anxiolytics, antidepressants, and other psychostimulants unless prescribed and stable for two months
(4) Current diagnosis of any severe psychiatric disorder.
(5) Any significant current medical condition such as neurological, cardiovascular, endocrine, renal, or hepatic pathology that would increase risk or would interfere with/mimic tobacco abstinence
(6) Known hypersensitivity to propylene glycol.
(7) Pregnant or lactating females.
(8) Uncontrolled asthma (defined as <20 on Asthma Control Test AND/OR endorsement of “yes” to environmentally induced bronchospasm that requires prescription Epipen
(9) Medical conditions, including chronic and untreated acute pulmonary conditions, that in the investigators view will increase risk of respiratory problems among participants
(10) Nut allergy or known allergy to e-liquids and/or their flavorants
(11) Report of greater than “without any difficulty” on any item of the PROMIS Physical Function Short Form
(14) 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
(15) Not fully vaccinated against COVID-19

Study 2:
Inclusion Criteria:
(1) Ages 21--50 years

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(2) Able to read and write
(3) Smoking cigarettes or cigars daily for at least the past 30 days (month)
(4) urine cotinine levels of at least 200ng/mL
(5) Willing to abstain from regular smoking for 2 weeks and use only e-cigs [Ad-lib portion of the study on hold; this inclusion criteria is ON HOLD until ad lib portion is resumed]
(6) Not seeking treatment to stop smoking
(7) Use of e-cigarettes at least 10 times in the past six months
(8) Do not plan to discontinue e-cigarette use
(9) Have not stopped use due to COVID
(10) Do not have a strong preference for a flavor or a device

Exclusion Criteria:
(1) Current criteria for moderate or severe cannabis and alcohol use disorder as per DSM-V criteria.
(2) Current criteria for mild, moderate or severe substance use disorder on any other psychoactive substances as per DSM-V criteria except for tobacco use disorder
(3) Use of psychoactive drugs including anxiolytics, antidepressants, and other psychostimulants unless prescribed and stable for two months
(4) Current diagnosis of any severe psychiatric disorder.
(5) Any significant current medical condition such as neurological, cardiovascular, endocrine, renal, or hepatic pathology that would increase risk or would interfere with/mimic tobacco abstinence
(6) Known hypersensitivity to propylene glycol.
(7) Pregnant or lactating females.
(8) Uncontrolled asthma (defined as <20 on Asthma Control Test AND/OR endorsement of "yes" to environmentally induced bronchospasm that requires prescription Epipen
(9) Medical conditions, including chronic and untreated acute pulmonary conditions, that in the investigators view will increase risk of respiratory problems among participants
(10) Nut allergy or known allergy to e-liquids and/or their flavorants
(11) Report of greater than "without any difficulty" on any item of the PROMIS Physical Function Short Form
(14) 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
(15) Not fully vaccinated against COVID-19

9. How will **eligibility** be determined, and by whom?
Eligibility for Study 1B :
Participants will complete consent. During this process, all limits to confidentiality will be clearly explained. Following this, the participants will meet with the research assistant to obtain initial assessments. Medical and substance abuse histories, urine drug and pregnancy tests, breath CO and urine cotinine levels will be obtained from all participants.
The genetics saliva samples will be collected at the time of physical exam from those who have consented to providing these samples. The samples will be stored in a -20-degree Celsius freezer prior to being de-identified and transported to Dr. Gelernter's lab.

Eligibility for Study 2:
Participants will complete consent, all questionnaires, medical history, and psychological evaluation remotely. If eligible following administration of remote intake, participants will come in for a very brief visit in which a brief physical and biochemical measure collection (including urine sample, carbon monoxide reading, blood pressure). If subject is suspected to be intoxicated at intake visit, a breathalyzer will be performed. If the BAC level is $\geq$ 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

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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.
As in Study 1, medical and substance abuse histories (including tobacco and marijuana use), urine drug and pregnancy tests, breath CO and urine cotinine levels will be obtained from all participants. All participants will receive a physical exam and a psychological evaluation to determine eligibility. If they have consented to genetic study, saliva will be obtained (2ml). 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.

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 lab sessions in Study 2, participants may experience symptoms of nicotine withdrawal, such as nicotine craving, mild anxiety, restlessness, irritability, difficulty concentrating, loss of energy and excessive hunger. These 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 screening, saliva, and urine collections should add no risks other than those normally associated with these procedures.

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. Our past experience with these measures indicates that they are acceptable to subjects.

Use of electronic cigarette: The requirement of having had experience with e-cigs reduces the risk for young adults in Study 1 from experiencing adverse reaction to an e-cig. Additionally, participants will have recent (past 30 day) e-cigarette use and must have urine cotinine levels indicating they use nicotine products (>200 ng/ml). This level of cotinine will indicate that participants are regular e-cigarette users and reduce the likelihood of adverse effects related to nicotine administration such as nausea, vomiting, and/or dizziness. Furthermore, in Study 1 we chose a nicotine concentration of 36mg/ml in a nicotine salt formulation (equivalent to 3.6%) as this is lower nicotine concentration than popular JUUL (5%) and disposeable e-cigarette device formulations (5-7%). We have used similar procedures with adult tobacco users. Subjects will be told that participation is voluntary, and they can stop anytime if they want to and/or if they experience adverse events from nicotine or flavor exposure. Additionally, participants will be offered light snacks to reduce the incidence of nausea from nicotine administration that may be heightened by administration of nicotine on an empty stomach.

In conducting this research, we will comply with applicable institutional, federal, state, and local requirements (including CDC and state of Connecticut guidelines), and other applicable policies regarding pauses and reactivation of in-person research, public health precautions (daily monitoring of COVID19 checks for staff, face masks, testing, etc.), and work precautions (physical distancing, shift work, use of PPE, etc.). Prior to implementation of the study, and in addition to receiving IRB approval, a request to activate/re-activate our study, including a review of our safety plan, will be submitted and approved by the Human Subject Research (HSR) Review Committee or the OffCampus Research and Fieldwork Committee (OCRFC) as applicable. In addition, the information in the "Research Participant Information Sheet - Important Information about the COVID-19 Pandemic and Research Participation" will be discussed with research participants prior to an in-person visit (and provided to the participant prior to a visit, if possible) and documented in the research participant and/or study file as appropriate.

In Study 2, the participants are current cigarette smokers, and are, therefore, already self-administering higher doses of nicotine (we will require cotinine > 200ng/mL). Also, we will use nicotine concentrations that are in the range commonly used by both younger and older combustible tobacco users should therefore, be sufficient to relieve nicotine withdrawal and have positive effects.
Participants will be informed about the following CDC information about vaping:

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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 shows 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.

The e-cigarettes and e-liquid pods that we will use in the current study are purchased only from a licensed retailer and do not contain CBD, THC, or Vitamin E Acetate. At this time, we don’t know what the risks associated with the use of the e-cigarettes and e-liquids, flavors, etc. that we use in this study are, and who might develop symptoms. The pods we are giving participants contain nicotine, solvents, and flavorings. We will ask participants to only use the e-cigarette pods provided and inform them not attempt to hack or modify the e-cigarette device in any way.

E-cigarettes contain other chemicals besides nicotine including propylene glycol/vegetable glycol/vegetable glycerin. At this time, we do not know the risks associated with the propylene glycol/ vegetable glycerin that may in the fillers in the liquids used in this study. However, there may be unforeseen risks (such as allergic reactions). Participants will be asked not to participate if they have known allergies to propylene glycol (a constituent in e-liquids), known allergies to any e-liquids flavorants, and/or nut allergies (as our e-liquids are made in a facility in which they could have come in contact with nuts). We will be using e-liquids that are freely available for purchase and the propylene glycol/vegetable glycerin doses will be what is available in these e-liquids. Some research has indicated that in large doses propylene glycol and vegetable glycerin can be harmful. All levels of e-liquids administered in this research study are below any potentially harmful levels. Additionally, participants may report the experience of a burning sensation or irritation during use of the e-cigarette. However,

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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.

We will assess your health at the intake to make sure you are healthy prior to participating and will continue to monitor your health closely during the study.

All participants will have an extensive medical history evaluation reviewed by the study APRN 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 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.

The lab sessions will be conducted by trained research staff who are sensitive to the smoking population and trained to monitor any potential adverse effects. Heart rate, blood pressure, and pulse oximetry will be assessed at baseline and every in-person visit for safety. If they experience any side effects or concerns during the study, we ask them to let us know. Participants will be told that they are able to stop the study at any point. If they feel any discomfort or need to stop for any reason, they can let the research team know. We will also provide participants with referral sources to quit smoking if they are interested.

Nicotine, menthol and sweet 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 participants 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 throat. The doses of menthol that are found in cough drops, ranging 1 to 10 mg are regarded to be safe (Sweetman, 2011). In spite of 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 sweet flavors 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.

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-cigs 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

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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.

11. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized. ***Recruitment and Informed Consent*** Recruitment for Study 1 will be conducted via a variety of methods. We will utilize Craigslist, flyers, Reddit, and social media to recruit. All participants recruited via Craigslist, flyers, Reddit, and social media will be referred to ongoing cessation studies or given cessation materials at the end of the current study.

Recruitment for Study 2 will be through advertisements on Craigslist, Facebook, flyers in the community, radio and novelties (e.g. matchbooks, bottle openers, tic tacs, coasters, etc). At the initial intake session, potential participants will sign informed consent and complete initial assessments. As in Study 1, medical and substance abuse histories, urine drug and pregnancy tests, breath CO and urine cotinine levels will be obtained from all participants. All participants will receive an extensive medical history evaluation reviewed by the study APRN and a psychological evaluation to determine eligibility. 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.

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? Minor increase over minimal risk

    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 ≥18 year old's
    - Requiring experience with e-cigs.
    - Using well-defined inclusion/exclusion criteria and physical exams and clinical psychological evaluations to rule pre-existing medical conditions.
    - Monitoring use of e-cigs and cigarettes at follow ups
    - Providing a motivational session with a clinical psychologist or licensed social worker at the end of all procedures to inform participants about the potential risks of e-cigarette and other tobacco use behaviors and to discourage using these products in the future.
    - Providing a motivational session with a clinical psychologist or licensed social worker at the end of Study 2 to encourage them to stop using with referral to tobacco treatment based on interest.
    - 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 young adults, as well as combustible tobacco users.
    - 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

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Cancer Center & Research Institute) and a statistical expert (Dr. Hanga Galfalvy, Assistant Professor of Neurobiology, Columbia University).

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 Investigators 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 PIs. PIs 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 Yale Qualtrics Database which will then be 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. Krishnan-Sarin and Dr. Green 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 and Yale Qualtrics. 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 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 undergo a psychological evaluation and a physical exam to determine their eligibility and safety of their participation in this study reviewed by a clinical psychologist (psychological evaluation) and a medical professional (physical exam)(see appendix for psych eval training SOP). Special attention will be placed on serious mental health issues not being treated and those at risk will be encouraged to seek mental health treatment. Participants will be terminated from participation if the investigator feels that their health or well-being may be threatened by continuation in the study. All participants in Study 1B will be given educational materials regarding potential risks of continued e-cigarette use, as well as resources for vaping cessation, at the conclusion of their lab

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session. We will specifically highlight the page that includes resources for treatment. All paticipants in Study 2 will receive a motivational interview following their participation to educate them about the potential risks from using tobacco products and to encourage them to abstain. If a participant from Study 2 shows interest in quitting use of any tobacco products, an appropriate referral will be made to one of our local smoking cessation programs. We will measure health status throughout the study by using self-report questionnaires to assess fatigue, dyspnea, asthma and overall health with a checklist of symptoms related to the reported vaping illnesses. These assessments will be administered at every in-person visit. We will also assess heart rate, blood pressure, and pulse oximetry at baseline and every in-person visit.

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. 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 investigators, Drs. Krishnan-Sarin and Green, 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 PIs will evaluate whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. If necessary, PIs will consult with study physician. Either the PIs 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 PIs 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 <u>which the Yale PI serves as the lead investigator</u>:

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*

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13. **Statistical Considerations:** Describe the statistical analyses that support the study design.
Power Calculations: Study 1: For Aim 1, we will recruit **40 subjects.** With an anticipated dropout of 10%, 36 subjects are expected to have complete data and thus we base our power calculation on this sample size. The repeated measures design (with all factors within-subject) provides 80% power at significance level 0.05 to detect an interaction of large effect size f=0.4 between nicotine and menthol on e-cigarette liking/disliking for sweet flavors.
Study 2: For Aim 2, we will recruit **120 subjects**: 30 younger and 30 older subjects randomized to 6mg/ml nicotine, 30 younger and 30 older to 18mg/ml. With an anticipated dropout of 10%, we base our power calculation on 108 subjects. This sample size provides 82% power at significance level 0.05 to detect an interaction of large effect size f=0.4 between age and flavor on e-cig liking/wanting at 18mg/ml nicotine. Similar effect sizes were observed in our previous e-cig study examining the interaction of nicotine and menthol [26].

Data Management: 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's 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: 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. A significance level of 0.05 will be used for primary outcomes and a Bonferroni correction will be applied for secondary outcomes.

Aim 1 (Study 1). Mixed-effects model will include menthol (yes, no), and measurement time (lab, time-within-lab). A combination of random effects and structured variance-covariance matrices will be used to account for within-subject correlations. The best-fitting structure will be selected based on Akaike information criterion (AIC). We also anticipate statistically significant main effects of menthol on liking. Similar models will be used for the secondary outcomes (flavor intensity, coolness, sweetness and harshness). Mixed models will be used to test whether menthol-related alleviation in harshness and improvement in liking (subject-specific difference between menthol and no-menthol scores) predicts percent days of nicotine-containing e-cig use at 1-month and follow up.

Aim 2 (Study 2). The mixed models will include age group (younger adults, older adults) and nicotine dose (6, 18mg/ml) as between-subject factors, flavor (menthol, vanilla, tobacco, cherry) as a within-subject factor, and measurement time (lab, time-within-lab). The models will also include all possible interactions among age, nicotine and flavor, and adjust for the stratification variables (sex and nicotine dependence). We will use the same strategy for modelling the correlation structure as in Aim 1. The primary hypothesis (in terms of liking/wanting, menthol preferred to sweet more in the younger than in the older subjects at 18 mg/ml nicotine) will be tested via linear contrasts. We also anticipate significant main effects of age and flavor on liking/wanting. Similar models will be used for secondary/exploratory outcomes (nicotine-induced stimulation, harshness and withdrawal; e-cigarette value). To examine flavor effects on use of different flavored e-cigs during the two-week ad-lib access period, for each subject we will compute the percent amount liquid used out of the total amount liquid they were given in each one of the three flavors. We will analyze these three outcomes together via a mixed model with flavor, age, and flavor-by-age interaction as predictors.

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

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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.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **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 radiotracer is being administered to humans, include relevant data on animal models.
Write here

5. **Source:** Identify the source of the radiotracer to be used. *Write here*

6. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

B. DRUGS/BIOLOGICS ☐N/A

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)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☒
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

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.
These devices are commercially available and therefore, we do not need an IND. We obtain all of our e-liquid from American eLiquid Store. The e-liquid mixture in Study 1 (propylene glycol [PG], vegetable glycerin [VG] and watermelon and watermelon-menthol flavorings 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. The

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e-liquid mixture in Study 2 (propylene glycol [PG], vegetable glycerin [VG] and tobacco, strawberry, 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. For Study 1, we will use 36mg/ml nicotine salt and for Study 2, we will use 6mg and 18 mg nicotine. 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.As the e-liquids used in Study 1 are not currently commercially available, an ITP will be sought and approved before study activities commence.

The 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-liquidswill 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. The vanilla ice e-liquids will be purchased from Mister E-Liquid located in Grand Rapids, Michigan. 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.

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

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. 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 lab 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, 2 and 3 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 in both studies. 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. The research staff will have the group randomization list and will dispense the appropriate e-liquid (nicotine level, flavor) needed for each subject.

Check applicable Investigational Drug Service utilized:

☐ **YNHH IDS** ☐ **CMHC Pharmacy** ☐ **West Haven VA**

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☐ **PET Center** ☐ **None**

☒ **Other: John Pierce Lab, WCRU (West Campus Research Unit)**

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

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study. *Write here*

c) Address the greatest potential harm that may come to a participant as a result of receiving placebo. *Write here*

d) Describe the procedures that are in place to safeguard participants receiving placebo. *Write here*

6. **Continuation of Drug Therapy After Study Closure ☒Not applicable to this project**

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ **Yes** If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ **NO** If no, explain why this is acceptable. *Write here*

B. DEVICES ☒N/A

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

***If Yes, please be aware of the following requirements*:**

A YNHH New Product/Trial Request Form must be completed via EPIC: **Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request**; AND

Your request must be reviewed and approved **in writing** by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. **Background Information:** Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   Write here
3. **Source:**
   a) Identify the source of the device to be used. *Write here*
   b) Is the device provided free of charge to subjects? ☐Yes ☐No

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4. **Investigational device accountability**: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

   a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): *Write here*

   b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): *Write here*

   c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: *Write here*

   d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: *Write here*

   e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: *Write here*

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. Targeted for enrollment at Yale for this protocol: Study 1: 40 subjects; Study 2: 120 subjects
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):	
☒ XOther: TrialFacts Recruitment Services; Qualtrics Online Sample		

* **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:

Describe how potential subjects will be identified. Potential subjects will be recruited through methods previously used by our team and found to be effective. Recruitment will occur via advertising at local colleges and through Craigslist, Facebook and flyers in the community. Potential subjects will also be recruited through Trialfacts. Trialfacts is a recruitment company that specializes in research recruitment services and has been utilized in the past by Yale investigators. Services include comprehensive pre-screening, advertising. Trialfacts creates recruitment materials, landing pages, digital marketing campaigns, online advertisements. Trialfacts adheres to GCP and IRB requirements.

We additionally plan to use Qualtrics Online Sample, as a potential recruiting source used successfully in prior studies by our group. Participants will be recruited directly through Qualtrics Online Sample, a secure, market research service operated by Qualtrics, Inc. In line with procedures we have used in prior studies, Qualtrics will email invitations to panelists who they deem likely to be eligible for the study based on prior responses to a demographics survey(s) administered by Qualtrics (or its affiliate panels)

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at the time participants became panelists (e.g., lifetime smoking status). Interested individuals will click on an embedded link, which will direct them to the study eligibility questions. Eligible and interested individuals will be contacted to schedule an intake appointment.

a. We also will include flyers that advertise that persons who complete the screener form (either through the Yale Qualtrics link or via phone) will be entered into a monthly raffle for a $50 Amazon e-gift card regardless of their eligibility status. This is to minimize the amount of blank/half-completed screeners we receive and to provide a benefit to participants who may find the screener a time burden. Monthly, all contact information will be separated from screener information into a list. Any duplicate information will be removed, and a random number generator will be used to determine the winner of the raffle. Winners will be contacted up to 3 times to inform them of their gift card winnings. If winners are not reached, then the process will be repeated to select a new winner. Non-winners will stay on the list and be eligible to win the raffle in the future. This recruitment process will be closely monitored and if not successful at producing increases in participation in the screener and eligible subjects, will be removed.

b. Describe how potential subjects are contacted. Potential participants can contact the study to determine eligibility through phone call, text message through Text Now, or a website that will direct them to a Yale Qualtrics website where interested participants can complete a brief screening questionnaire. In addition to general screening questions, they will be asked questions regarding where they see e-cigarette ads on social media to assist with future recruitment as well as provide necessary data showing how companies are using social media to advertise. 'Microsoft Teams' will be used to maintain these screening records. If recruited via TrialFacts, participants will be scheduled via Trialfacts to receive a phone call via our Team.

c. 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

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team, participants will provide verbal consent for the screening process. If participants prefer to complete the online screener through the Yale Qualtrics system, participants will provide signed consent in the online screening.

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.

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, via phone or video conferencing depending on technological capabilities of participant) 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**.** If the participant has limited internet access, a consent form will be mailed to them. The entire consent form will be reviewed in detail with the participant in a private, one-on-one setting at the first intake appointment. All risks and potential benefits will be described. Any questions the participant may have will be addressed. If the participant wishes, they may 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.

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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 <u>signed</u> 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.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒
  - Why would the research be impracticable to conduct without the waiver? 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.
  - Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? At the first phone contact with the research team, participants will provide verbal consent for the screening process. Participants who meet initial eligibility during the screening process will be invited for an in-person meeting to learn more about the study, ask any questions, and provide written informed consent before beginning research activities.

☐ Requesting a waiver of consent:

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

☐ <u>Entire Study</u>

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

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

2. 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. Patient health information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Compound Consent and Authorization form signed by the patient or unless permitted or required by law.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other
   Digital data with PHI will be stored on a secured server. Digital data without PHI may be stored and analyzed on a laptop or desktop computer.

4. 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? 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

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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

5. 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.

6. 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.)
The proposed project will provide the FDA with important data regarding the influence of flavors on the abuse potential of e-cigs in adults. The e-cig provides the user with the opportunity to manipulate nicotine content and flavors, which might be attractive to young adult smokers. Thus, it is imperative that we fully understand what young smokers find appealing about this product because such a product has the ability to become widely used. The use of e-cigs is increasing and could become a future epidemic among young users with potentially harmful health consequences. Developing an understanding of how sweet and cool flavors influence appeal among young adults who are susceptible to future e-cigarette use is crucial to the regulation of the constituents of existing and future modified risk tobacco products. Additionally, addressing whether sweet, cool and tobacco flavors differentially alter nicotine reward and use of e-cigs among younger and older adult combustible tobacco users who might be trying to switch to e-cigarettes for harm-reduction is important. Older combustible tobacco users may not need flavors to increase the palatability of tobacco products and to benefit from switching to e-cigs. The goals of this project are to develop a comprehensive understanding of flavors and other tobacco constituents on nicotine's addictive potential and the appeal and use of tobacco products.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Write here
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.
   As an economic consideration, we will compensate participants for time spent in this research project.

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Participants in Study 1 (n=40) will receive $50 for the intake, $100 for the Lab visit, and $25 cash/Amazon gift card for the the follow up visits (1 month). Participants can be compensated up to $20/in person visit for travel (up to $40). Thus, each participant can earn up to $215 for Study 1.

Participants may earn a $25 referral bonus for each friend that is referred to participate in this study. In order to receive this bonus, the friend(s) must complete the intake appointment and physical exam.

Participants in Study 2 will receive $50 for Intake and $25 for in-person intake. If ineligible after intake, participants will receive compensation in the form of an electronic gift card of their choosing (examples include but are not limited to Amazon, Wal-Mart, Target, Stop & Shop). If they do not have an email account, a gift card will be mailed to them. Participants in Study 2 (n=120) will receive escalating payments per lab session to increase completion ($50 for Lab 1, $75 for Lab 2, $100 for Lab 3, $125 for Lab 4) and a $25 gift card for each of the follow up visits (1 month, 6 month).
Both studies will compensate participants $20/day for travel to appointments after the initial intake (up to $100, follow ups will conducted over the phone). Thus, each participant in Study 1 can earn a total of $215 (including value of gift cards) and each participant in Study 2 can earn up to $575 (including value of gift cards). If participants have borrowed a study cell phone from us for the study, we will ask that they return the cell phone at the last visit. The final visit payment will be withheld until the cell phone is returned. Participants enrolled in the study will be paid via cash or in some cases (see above) gift cards. As the ad-lib portion of Study 2 is on hold, participants will not receive payments associated with the ad-lib portion of the study (i.e. compensation for daily CosCOs, questionnaires, ad-lib visits, as well as returning the e-cigarette and battery.

Participants may earn a $25 referral bonus for each friend that is referred to participate in this study. In order to receive this bonus, the friend(s) must complete the intake appointment and physical exam.

We will validate parking in the Air Rights parking garage. We will provide round trip cab transportation to appointments after the remote intake, if transportation is an issue.

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

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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 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. Talhout R, van de Nobelen S, Kienhuis AS. An inventory of methods suitable to assess additive-induced characterising flavours of tobacco products. *Drug and alcohol dependence.* 2016;161:9-14.
2. Rosbrook K, Green BG. Sensory Effects of Menthol and Nicotine in an E-Cigarette. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016;18(7):1588-1595.
3. Krishnan-Sarin S, Green, B.G., Jordt, S.E., O'Malley, S.S. . The Science of Flavor in Tobaco Products; A report presented to the WHO Global Tobacco Regulators Forum. Tob Reg Technical Report Series: World Health Organization; 2017.
4. Krishnan-Sarin S, Green, B.G., Kong, G., Cavallo, D.A., Jatlow, P., Gueorguieva, R., Buta, E., O'Malley, S.S. Studying the interactive effects of menthol and nicotine among youth: an examination using e-cigarettes. *Drug and alcohol dependence.* 2017;180:193-199.
5. Green BG. Chemesthesis: Pungency as a component of flavor. *Trends in Food Science & Technology.* 1996;7:415-420.

6. Giovino GA, Sidney S, Gfroerer JC, et al. Epidemiology of menthol cigarette use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2004;6 Suppl 1:S67-81.
7. Menthol cigarettes and public health: review of the scientific evidence and recommendations. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pd.
8. Green BG. Menthol modulates oral sensations of warmth and cold. *Physiology & behavior.* 1985;35(3):427-434.
9. Green BG. The sensory effects of l-menthol on human skin. *Somatosensory & motor research.* 1992;9(3):235-244.
10. Eccles R. Menthol: effects on nasal sensation of airflow and the drive to breathe. *Current allergy and asthma reports.* 2003;3(3):210-214.
11. Andersson DA, Chase HW, Bevan S. TRPM8 activation by menthol, icilin, and cold is differentially modulated by intracellular pH. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2004;24(23):5364-5369.
12. Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored Tobacco Product Use Among Middle and High School Students--United States, 2014. *MMWR Morbidity and mortality weekly report.* 2015;64(38):1066-1070.
13. Villanti AC, Johnson AL, Ambrose BK, et al. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014). *American journal of preventive medicine.* 2017.
14. Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *Jama.* 2015;314(17):1871-1873.
15. King BA, Dube SR, Tynan MA. Flavored cigar smoking among U.S. adults: findings from the 2009-2010 National Adult Tobacco Survey. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2013;15(2):608-614.
16. King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine.* 2014;54(1):40-46.
17. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2015;17(7):847-854.
18. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tobacco control.* 2016;25(Suppl 2):ii62-ii66.
19. Klein SM, Giovino GA, Barker DC, Tworek C, Cummings KM, O'Connor RJ. Use of flavored cigarettes among older adolescent and adult smokers: United States, 2004--2005. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2008;10(7):1209-1214.
20. Hoffman AC, Salgado RV, Dresler C, Faller RW, Bartlett C. Flavour preferences in youth versus adults: a review. *Tobacco control.* 2016;25(Suppl 2):ii32-ii39.
21. Cooper M, Harrell MB, Perry CL. A Qualitative Approach to Understanding Real-World Electronic Cigarette Use: Implications for Measurement and Regulation. *Preventing chronic disease.* 2016;13:E07.
22. Kistler CE, Crutchfield TM, Sutfin EL, et al. Consumers' Preferences for Electronic Nicotine Delivery System Product Features: A Structured Content Analysis. *International journal of environmental research and public health.* 2017;14(6).
23. Czoli CD, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: results from a discrete choice experiment. *Tobacco control.* 2016;25(e1):e30-36.
24. Chen C, Zhuang YL, Zhu SH. E-Cigarette Design Preference and Smoking Cessation: A U.S. Population Study. *American journal of preventive medicine.* 2016;51(3):356-363.

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25. Meier E, Isaksson Vogel R, O'Connor RJ, Severson HH, Shields PG, Hatsukami DK. Preference for Flavored Noncombustible Nicotine Products Among Smokers Motivated to Switch From Cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016;18(5):892-893.
26. Bold KW, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. E-cigarette susceptibility as a predictor of youth initiation of e-cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016.
27. Lim J, Wood A, Green BG. Derivation and evaluation of a labeled hedonic scale. *Chemical senses.* 2009;34(9):739-751.
28. Morean M, Butler EW, Bold KW, et al. Preference for more e-cigarette flavors is associated with e-cigarette use frequency among youth but not adults. Paper presented at: Society for Research on Nicotine and Tobacco2017; Florence, Italy.
29. NACDAa. Guidelines for Administration of Drugs to Human Subjects. 2006; https://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-administration-drugs-to-human-subjects.
30. NACDAb. Guidlines for Substance Abuse Research Involving Children and Adolescents. 2012; https://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-substance-abuse-research-involving-children-adolescents.
31. Green BG, Shaffer GS, Gilmore MM. Derivation and Evaluation of a Semantic Scale of Oral Sensation Magnitude with Apparent Ratio Properties. *Chemical senses.* 1993;18:683-702.
32. Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J. Evaluating the 'Labeled Magnitude Scale' for measuring sensations of taste and smell. *Chemical senses.* 1996;21(3):323-334.
33. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *Journal of consulting and clinical psychology.* 2000;68(1):134-144.
34. Toll BA, Cooney NL, McKee SA, O'Malley SS. Correspondence between Interactive Voice Response (IVR) and Timeline Followback (TLFB) reports of drinking behavior. *Addictive behaviors.* 2006;31(4):726-731.
35. Collins SE, Eck S, Torchalla I, Schroter M, Batra A. Validity of the timeline followback among treatment-seeking smokers in Germany. *Drug and alcohol dependence.* 2009;105(1-2):164-167.
36. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and alcohol dependence.* 1996;42(1):49-54.
37. Lewis-Esquerre JM, Colby SM, Tevyaw TO, Eaton CA, Kahler CW, Monti PM. Validation of the timeline follow-back in the assessment of adolescent smoking. *Drug and alcohol dependence.* 2005;79(1):33-43.
38. Soria R, Stapleton JM, Gilson SF, Sampson-Cone A, Henningfield JE, London ED. Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers. *Psychopharmacology.* 1996;128(3):221-226.
39. Griffiths RR, Troisi JR, Silverman K, Mumford GK. Multiple-choice procedure: an efficient approach for investigating drug reinforcement in humans. *Behavioural pharmacology.* 1993;4(1):3-13.
40. Krishnan-Sarin S, Cavallo DA, Cooney JL, et al. An exploratory randomized controlled trial of a novel high-school-based smoking cessation intervention for adolescent smokers using abstinence-contingent incentives and cognitive behavioral therapy. *Drug and alcohol dependence.* 2013;132(1-2):346-351.
41. Krishnan-Sarin S, Duhig AM, McKee SA, et al. Contingency management for smoking cessation in adolescent smokers. *Experimental and clinical psychopharmacology.* 2006;14(3):306-310.
42. Staley JK, Krishnan-Sarin S, Cosgrove KP, et al. Human tobacco smokers in early abstinence have higher levels of beta2* nicotinic acetylcholine receptors than nonsmokers. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006;26(34):8707-8714.
42. Cosgrove KP, Esterlis I, McKee SA, et al. Sex differences in availability of beta2*-nicotinic acetylcholine receptors in recently abstinent tobacco smokers. *Archives of general psychiatry.* 2012;69(4):418-427.

APPROVED BY THE YALE UNIVERSITY IRB 4/12/2023

43. Cosgrove KP, Esterlis I, McKee S, et al. Beta2* nicotinic acetylcholine receptors modulate pain sensitivity in acutely abstinent tobacco smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2010;12(5):535-539.
44. Kong G, Goldberg A, Dallery J, Krishnan-Sarin S. An Open-Label Pilot Study of a Smoking Cessation Intervention Using Mobile Phones to Deliver Contingency Management to High School Students. *Experimental and clinical psychopharmacology.* in press.
45. Morean ME, de Wit H, King AC, Sofuoglu M, Rueger SY, O'Malley SS. The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology.* 2013;227(1):177-192.
46. Bauman KE, Koch GG, Bryan ES, Haley NJ, Downton MI, Orlandi MA. On the measurement of tobacco use by adolescents. Validity of self-reports of smokeless tobacco use and validity of cotinine as an indicator of cigarette smoking. *American journal of epidemiology.* 1989;130(2):327-337.
47. Schick SF, Blount BC, Jacob P, 3rd, et al. Biomarkers of Exposure to New and Emerging Tobacco and Nicotine Delivery Products. *American journal of physiology Lung cellular and molecular physiology.* 2017:ajplung.00343.02016.
48. Shadel WG, Edelen MO, Tucker JS, Stucky BD, Hansen M, Cai L. Development of the PROMIS nicotine dependence item banks. *Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco.* 2014;16(Suppl 3):S190-201.
49. Morean M, Krishnan-Sarin S, Sussman S, et al. Psychometric evaluation of the Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for use with electronic cigarettes. *Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco.* under reivew.
50. Pierce JP, Choi WS, Gilpin EA, Farkas AJ, Merritt RK. Validation of susceptibility as a predictor of which adolescents take up smoking in the United States. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 1996;15(5):355-361.
51. Chen QY, Alarcon S, Tharp A, Ahmed OM, Estrella NL, Greene TA, Rucker J, Breslin PA. Perceptual variation in umami taste and polymorphisms in TAS1R taste and receptor genes. *The American journal of clinical nutrition.* 2009; 90(3):770S-779S.
52. Breslin PA. Human gustation. In: Finger TE, Silver WL, Restrepo D, editors. The neurobiology of taste and smell. 2000. New York: Wiley-Liss. 423–461.
53. Fushan AA, Simons CT, Slack JP, Drayna D. Association between common variation in genes encoding sweet taste signaling components and human sucrose perception. *Chemical senses.* 2012; 35(7);579-592.
54. Jensen KP, DeVito EE, Herman AI, Valentine GW, Gelernter J, Sofuoglu M. A CHRNA5 smoking risk variant decreases the aversive effects of nicotine in humans. *Neuropsychopharmacology.* 2015; 40(12):2813-2821.
55. Rawal S, Hayes JE, Wallace MR, Bartoshuk LM, Duffy VB. Do polymorphisms in the TAS1R1 gene contribute to broader differences in human taste intensity? *Chemical senses.* 2013; 38(8):719-728.
56. Risso DS, Kozlitina J, Sainz E, Gutierrez J, Wooding S, Getachew B, Luiselli D, Berg CJ, Drayna D. Genetic variation in the TAS2R38 bitter taste receptor and smoking behaviors. *PLoS One.* 2016; 11(10):e0164157.

1. Rosbrook K, Green BG. Sensory Effects of Menthol and Nicotine in an E-Cigarette. *Nicotine Tob Res.* 2016;18(7):1588-1595.
2. Soria R, Stapleton JM, Gilson SF, Sampson-Cone A, Henningfield JE, London ED. Subjective and cardiovascular effects of intravenous nicotine in smokers and non-smokers. *Psychopharmacology (Berl).* 1996;128(3):221-226.
3. Griffiths RR, Troisi JR, Silverman K, Mumford GK. Multiple-choice procedure: an efficient approach for investigating drug reinforcement in humans. *Behav Pharmacol.* 1993;4(1):3-13.

4. Green BG. Chemesthesis: Pungency as a component of flavor. *Trends in Food Science & Technology.* 1996;7:415-420.
5. Giovino GA, Sidney S, Gfroerer JC, et al. Epidemiology of menthol cigarette use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2004;6 Suppl 1:S67-81.
6. Menthol cigarettes and public health: review of the scientific evidence and recommendations. 2011. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM247689.pd.
7. Green BG. Menthol modulates oral sensations of warmth and cold. *Physiology & behavior.* 1985;35(3):427-434.
8. Green BG. The sensory effects of l-menthol on human skin. *Somatosensory & motor research.* 1992;9(3):235-244.
9. Eccles R. Menthol: effects on nasal sensation of airflow and the drive to breathe. *Current allergy and asthma reports.* 2003;3(3):210-214.
10. Andersson DA, Chase HW, Bevan S. TRPM8 activation by menthol, icilin, and cold is differentially modulated by intracellular pH. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2004;24(23):5364-5369.
11. Krishnan-Sarin S, Green, B.G., Jordt, S.E., O'Malley, S.S. . The Science of Flavor in Tobaco Products; A report presented to the WHO Global Tobacco Regulators Forum. In. Tob Reg Technical Report Series: World Health Organization; 2017.
12. Corey CG, Ambrose BK, Apelberg BJ, King BA. Flavored Tobacco Product Use Among Middle and High School Students--United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2015;64(38):1066-1070.
13. Villanti AC, Johnson AL, Ambrose BK, et al. Flavored Tobacco Product Use in Youth and Adults: Findings From the First Wave of the PATH Study (2013-2014). *American journal of preventive medicine.* 2017.
14. Ambrose BK, Day HR, Rostron B, et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA.* 2015;314(17):1871-1873.
15. King BA, Dube SR, Tynan MA. Flavored cigar smoking among U.S. adults: findings from the 2009-2010 National Adult Tobacco Survey. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2013;15(2):608-614.
16. King BA, Tynan MA, Dube SR, Arrazola R. Flavored-little-cigar and flavored-cigarette use among U.S. middle and high school students. *J Adolesc Health.* 2014;54(1):40-46.
17. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res.* 2015;17(7):847-854.
18. Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tobacco control.* 2016;25(Suppl 2):ii62-ii66.
19. Klein SM, Giovino GA, Barker DC, Tworek C, Cummings KM, O'Connor RJ. Use of flavored cigarettes among older adolescent and adult smokers: United States, 2004--2005. *Nicotine Tob Res.* 2008;10(7):1209-1214.
20. Hoffman AC, Salgado RV, Dresler C, Faller RW, Bartlett C. Flavour preferences in youth versus adults: a review. *Tobacco control.* 2016;25(Suppl 2):ii32-ii39.
21. Cooper M, Harrell MB, Perry CL. A Qualitative Approach to Understanding Real-World Electronic Cigarette Use: Implications for Measurement and Regulation. *Preventing chronic disease.* 2016;13:E07.
22. Kistler CE, Crutchfield TM, Sutfin EL, et al. Consumers' Preferences for Electronic Nicotine Delivery System Product Features: A Structured Content Analysis. *Int J Environ Res Public Health.* 2017;14(6).
23. Czoli CD, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: results from a discrete choice experiment. *Tobacco control.* 2016;25(e1):e30-36.

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24. Chen C, Zhuang YL, Zhu SH. E-Cigarette Design Preference and Smoking Cessation: A U.S. Population Study. *American journal of preventive medicine.* 2016;51(3):356-363.
25. Meier E, Isaksson Vogel R, O'Connor RJ, Severson HH, Shields PG, Hatsukami DK. Preference for Flavored Noncombustible Nicotine Products Among Smokers Motivated to Switch From Cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2016;18(5):892-893.
26. Krishnan-Sarin S, Green, B.G., Kong, G., Cavallo, D.A., Jatlow, P., Gueorguieva, R., Buta, E., O'Malley, S.S. Studying the interactive effects of menthol and nicotine among youth: an examination using e-cigarettes. *Drug and alcohol dependence.* 2017;in press.
27. Krishnan-Sarin S, Cavallo DA, Cooney JL, et al. An exploratory randomized controlled trial of a novel high-school-based smoking cessation intervention for adolescent smokers using abstinence-contingent incentives and cognitive behavioral therapy. *Drug and alcohol dependence.* 2013;132(1-2):346-351.
28. Krishnan-Sarin S, Duhig AM, McKee SA, et al. Contingency management for smoking cessation in adolescent smokers. *Exp Clin Psychopharmacol.* 2006;14(3):306-310.
29. Staley JK, Krishnan-Sarin S, Cosgrove KP, et al. Human tobacco smokers in early abstinence have higher levels of beta2* nicotinic acetylcholine receptors than nonsmokers. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2006;26(34):8707-8714.
30. Cosgrove KP, Esterlis I, McKee SA, et al. Sex differences in availability of beta2*-nicotinic acetylcholine receptors in recently abstinent tobacco smokers. *Archives of general psychiatry.* 2012;69(4):418-427.
31. Cosgrove KP, Esterlis I, McKee S, et al. Beta2* nicotinic acetylcholine receptors modulate pain sensitivity in acutely abstinent tobacco smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2010;12(5):535-539.
32. Kong G, Goldberg A, Dallery J, Krishnan-Sarin S. An Open-Label Pilot Study of a Smoking Cessation Intervention Using Mobile Phones to Deliver Contingency Management to High School Students. *Experimental and clinical psychopharmacology.* in press.
33. Fals-Stewart W, O'Farrell TJ, Freitas TT, McFarlin SK, Rutigliano P. The timeline followback reports of psychoactive substance use by drug-abusing patients: psychometric properties. *Journal of consulting and clinical psychology.* 2000;68(1):134-144.
34. Sobell LC, Brown J, Leo GI, Sobell MB. The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug and alcohol dependence.* 1996;42(1):49-54.
35. Toll BA, Cooney NL, McKee SA, O'Malley SS. Correspondence between Interactive Voice Response (IVR) and Timeline Followback (TLFB) reports of drinking behavior. *Addictive behaviors.* 2006;31(4):726-731.
36. Lewis-Esquerre JM, Colby SM, Tevyaw TO, Eaton CA, Kahler CW, Monti PM. Validation of the timeline follow-back in the assessment of adolescent smoking. *Drug and alcohol dependence.* 2005;79(1):33-43.
37. Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J. Evaluating the 'Labeled Magnitude Scale' for measuring sensations of taste and smell. *Chem Senses.* 1996;21(3):323-334.
38. Lim J, Wood A, Green BG. Derivation and evaluation of a labeled hedonic scale. *Chem Senses.* 2009;34(9):739-751.
39. Morean ME, de Wit H, King AC, Sofuoglu M, Rueger SY, O'Malley SS. The drug effects questionnaire: psychometric support across three drug types. *Psychopharmacology.* 2013;227(1):177-192.
40. Soler X, Holbrook JT, Gerald LB, et al. Validity of the Asthma Control Test Questionnaire Among Smoking Asthmatics. *J Allergy Clin Immunol Pract.* 2018;6(1):151-158.
41. Ameringer S, Elswick RK, Jr., Menzies V, et al. Psychometric Evaluation of the Patient-Reported Outcomes Measurement Information System Fatigue-Short Form Across Diverse Populations. *Nurs Res.* 2016;65(4):279-289.
42. Bauman KE, Koch GG, Bryan ES, Haley NJ, Downton MI, Orlandi MA. On the measurement of tobacco use by adolescents. Validity of self-reports of smokeless tobacco use and validity of

cotinine as an indicator of cigarette smoking. *American journal of epidemiology.* 1989;130(2):327-337.
43. Schick SF, Blount BC, Jacob P, 3rd, et al. Biomarkers of Exposure to New and Emerging Tobacco and Nicotine Delivery Products. *American journal of physiology Lung cellular and molecular physiology.* 2017:ajplung.00343.02016.
44. Shadel WG, Edelen MO, Tucker JS, Stucky BD, Hansen M, Cai L. Development of the PROMIS nicotine dependence item banks. *Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco.* 2014;16(Suppl 3):S190-201.
45. Morean M, Krishnan-Sarin S, Sussman S, et al. Psychometric evaluation of the Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for use with electronic cigarettes. *Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco.* under reivew.
46. Duhig AM, Cavallo DA, McKee SA, George TP, Krishnan-Sarin S. Daily patterns of alcohol, cigarette, and marijuana use in adolescent smokers and nonsmokers. *Addictive behaviors.* 2005;30(2):271-283.
47. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3(1):7-16.
48. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* 1986;43(3):289-294.
49. NACDAa. Guidelines for Administration of Drugs to Human Subjects. 2006; https://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-administration-drugs-to-human-subjects.
50. NACDAb. Guidlines for Substance Abuse Research Involving Children and Adolescents. 2012; https://www.drugabuse.gov/funding/clinical-research/nacda-guidelines-substance-abuse-research-involving-children-adolescents.

Appendix
Psychological Evaluation: Standard Operating Procedure

Relevant eligibility criteria to be assessed by psychological evaluation:

1. Current criteria for moderate or severe cannabis or alcohol use disorder as per DSM-V criteria
2. Current criteria for mild moderate or severe substance use disorder on any other psychoactive substances as per DSM-V criteria except for tobacco use disorder.
3. Use of psychoactive drugs including anxiolytics, antidepressants, and other psychostimulants unless prescribed and stable for two months
4. Current diagnoses of any severe psychiatric disorder.

Introduction:

- Introduce yourself to participant (if applicable), explain the purpose of this portion of the intake (to assess brief mental health and substance use history to assess participant's psychiatric health history and safety before participating in our study).
- Note that you will ask some questions that are sensitive about drug, alcohol, and psychiatric history, but all information will be kept confidential and only shared with team members as necessary for the study
- Capture current living situation (e.g., with whom and where) and employment (document on Psychological Evaluation Form).
- Ask participants hobbies, other activities they do outside of employment, family life.

For Substance Use eligibility criteria (1 & 2):

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- Collect tobacco use history, including what products they use. For each product, obtain age of initiation, current use frequency, products currently used, desire to quit, past quit experience [e.g., when, for how long]). Document on Psychological Evaluation Form.
- Assess ever use of alcohol, cannabis, stimulants, opioids, inhalants, PCP, hallucinogens, other substance.
- Collect details of ever self-reported drug and alcohol use (age of initiation, quantity, frequency, most recent use, any current use). Document on Psychological Evaluation Form.
- If past 12 month use of any of the above, assess presence and severity of SUD using SCID-RV (for DSM-5).
- If applicable, following eval, confirm with Research Assistant conducting the intake that self-report of substance use matches the medical history reported.

For Psychiatric criteria (3 & 4):

- Ask participant for a brief mental health history. Specifically obtain any diagnoses, both formal or informal, length of symptoms, treatment(s) if any, and any current symptoms of psychiatric conditions.
- For current conditions, determine if participant has untreated symptoms associated with conditions (e.g. symptoms of depression, but no medication or therapy indicated).
- Assess any current medications (including sleep disturbances) and reasons for use. Document if taking any for less than 2 months.

Assessment of suicide/homicide risk:

Suicide Risk:

- Utilize Beck Depression Inventory, Question 9 to assess suicidality.
- Preface by stating you are going to discuss suicidal thoughts and intentions. Acknowledge that these can be sensitive questions and reaffirm confidentiality if needed.
- Ask participant “Which of the following statements best describes how you feel *right now*?”
    - 0. “I don’t have thoughts of killing/hurting yourself”
    - 1. “I have thoughts of killing myself, but I would not carry them out”
    - 2. “I would like to kill myself”
    - 3. “I would kill myself if I got the chance”
- If greater than “0” above, assess:
    - Description (e.g. “What are your thoughts”; “Tell me about your thoughts?”)
    - The timeframe of feelings (when the most recent feelings were and when they first started)
    - How often these thoughts occur (“How often do these thoughts occur?)
    - Assess intention/plan (if not already reported)
        - Ask participant if they have thought about a plan (e.g. “Do you have a plan in place for this?” “Have you decided how or when you would kill yourself?”; “Have you worked out a plan for this?”)
        - If yes, assess plan and assess if they have the means (e.g. If they endorse use of gun, assess if they have access to a gun)
    - Previous attempts (“Have you had a suicide attempt in the past?”; get date(s))
    - Assess support system (e.g. who in their life they can discuss these feelings with) and if participant has strategies when these feelings occur (e.g. Do they have a way to keep themselves safe, such as talking to their support system).
- Deem if at immediate risk (e.g. indicating 2 or 3 or in follow up indicate current plan/intentions)

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    - If at immediate risk, keep participant on the zoom/in person and encourage them to seek further help (e.g. going to the emergency room, calling 211 while you stay on the zoom/in room). Offer to call on their behalf while they are on the Zoom as well.
    - Text/call Dana Cavallo (cell #: 203-610-9788) or Grace Kong (cell #: 646-236-3061)
    - If participant is at immediate risk and exits zoom, contact supervisors to determine plan of action. Contact participant's emergency contact.
- If not at immediate risk, offer list of support services (confirm RA can text them list, have list available in text) and let participant know they can contact us if they have questions or would like a referral to support services. Offer/ask if participant is comfortable with being referred to senior clinician on staff (avoid term "supervisor").

Homicide Risk:

- Ask participant: "Do you have any thoughts of hurting or harming others?"
- If yes, assess:
    - Description (e.g. "What are your thoughts"; "Tell me about your thoughts?")
    - Timeframe of feelings, who feelings are about (specific person, do not need to get name, but do determine if specific person), How often these thoughts occur, intentions (e.g. "What would you do?"; "when would you do it?")
    - Assess intention/plan (if not already reported)
        - Ask participant if they have thought about a plan (e.g. "Do you have a plan in place for this?" "Have you decided how or when?"; "Have you worked out a plan for this?")
        - If yes, assess plan and assess if they have the means (e.g. If they endorse use of gun, assess if they have access to a gun)
    - Assess support system (e.g. who in their life they can discuss these feelings with) and if participant has strategies when these feelings occur (e.g. Do they have a way to keep others safe such as talking to their support system).
    - If at risk of harming other (express intentions/plan), follow up with team to determine action plan.
    - If immediate risk, text/call Dana Cavallo (cell #: 203-610-9788) or Grace Kong (cell #: 646-236-3061).

Additional Information:

- Collect any additional information from participant, such as legal history if that is relevant.
- Thank participant for their time and willingness to share.

Post Evaluation:

- Save Psychological Evaluation form and accompanying paperwork (i.e. SCID) in (Z:\E-cig and Flavors Project 2 (TCORS2)\Data\Study 2\Study 2 Psych Evals to be signed) and email Grace Kong & Dana Cavallo that there is a psych evaluation for review. If second opinion is needed for eligibility or safety reasons, inform them that it is urgent.
- Determine eligibility and confirm to research assistant (if applicable).
- Save signed documentation in shared drive in participant folder.

Tips:

- Try to ask open-ended questions, so they cannot say give "No" type answer.

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- Don’t make people feel alienated for their drug/psych use (e.g. for reference points for frequency of always over-exaggerate; never appearing shocked or surprised by report).
- You shouldn’t feel like you’re are doing this alone. Don’t hesitate to get additional feedback. If you have any concern or worry, don’t be afraid to ask.

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