CENIC II PROJECT 2

The Impact of Cigarette Nicotine Content, E-Cigarette Nicotine Content and E-Cigarette Flavoring on Smoking Behavior

Principal Investigator:
Eric Donny, Ph.D.
Department of Physiology and Pharmacology
[redacted]

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Co-Investigator:
Caroline Cobb, PhD – VCU

Site Leaders:
Eric Donny, PhD – WFSOM
Andrew Strasser, PhD – Penn

Medical Monitors:
Claudia Campos, MD – WFSOM
John Spangler, MD - WFSOM

Biostatistician:

Joe Koopmeiners, PhD – UMN

Principal Investigator Contact Information:

Name: Eric Donny, PhD

Mailing Address: Dept of Physiology & Pharmacology, [redacted]

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Abbreviations

AE: **Adverse Events**: any untoward medical occurrence in a subject administered a study product and which does not necessarily have a causal relationship with this treatment.

BrAC: **Breath Alcohol Concentration**: measured by an expired breath sample, commonly used as a metric of alcohol exposure.

BDI: **Beck Depression Inventory, 2nd Edition**: a 21-question multiple-choice self-report inventory, used for measuring the severity of depression.

BP: **Blood Pressure:** is one of the principal vital signs.

BPM: **Beats Per Minute:** is one of the principal vital signs.

CDC: **Centers for Disease Control and Prevention**

CEMA: N-acetyl-S-(2-cyanoethyl)cysteine; mercapturic acid metabolite of acrylonitrile

CENIC: **Center for the Evaluation of Nicotine in Cigarettes:** the short title selected for this program grant that would be easily recognized.

CES: **Cigarette Evaluation Scale:** a 12-item questionnaire that assesses the degree to which smokers experience the reinforcing effects of smoking.

CES-D: **Center for Epidemiological Studies Depression Scale:** is a self-report measure of depression severity.

CO: **Carbon Monoxide:** exhaled breath carbon monoxide level reflects the level of carboxyhemoglobin (HbCO) in blood.

COPD: **Chronic Obstructive Pulmonary Disease:** is a type of obstructive lung disease characterized by chronically poor airflow.

CPD: **Cigarettes Per Day:** the amount of cigarettes smoked per day.

CTSI: **Clinical and Translational Science Institute**

DSMB: **Data Safety Monitoring Board**

ENDS: **Electronic Nicotine Delivery Systems:** products such as e-cigarette and vaping devices.

FDA: **Food and Drug Administration**

HR: **Heart Rate:** a measure of the number of heart beats per minute (bpm)

IVR: **Interactive Voice Response:** is a technology that allows a computer to interact with humans through the use of voice and input via keypad.

MNWS: **Minnesota Nicotine Withdrawal Scale**: is a 15-item self-reported scale to evaluate the effects of smoking cessation.

NIDA: **National Institute on Drug Abuse:** part of the National Institutes of Health whose mission is to "lead the Nation in bringing the power of science to bear on drug abuse and addiction."

NMR: **Nicotine Metabolite Ratio:** is a salivary measure of the ratio of nicotine metabolites, which indicates speed of nicotine metabolism.

NNC: **Normal Nicotine Content**

PATH: **Population Assessment of Tobacco and Health:** a longitudinal study national study looking at tobacco use and health.

PI: **Principal Investigator:** is the lead scientist for a particular, well-defined research project, such as a laboratory study or clinical trial.

PPM: **Parts Per Million**

REDCap: **Research Electronic Data Capture (web based software):** is a secure, web-based application for building and managing online surveys and databases.

SAE: **Serious Adverse Events:** generally, any event which causes death, permanent damage, birth defects, is life-threatening or requires hospitalization is considered an SAE.

SAETRS: **Serious Adverse Event Tracking and Reporting System**

TLFB: **Timeline Followback:** is a method that can be used as a clinical and research tool to obtain a variety of quantitative estimates of marijuana, cigarette, and other drug use by asking clients to retrospectively estimate their usage prior to the interview date.

TNE: **Total nicotine equivalents:** a urinary measure of nicotine and its metabolite concentrations.

VLNC: **Very low nicotine content:** cigarettes with much lower levels of nicotine than normal cigarettes (possibly below addictive levels).

WISDM: **Wisconsin Inventory of Smoking Dependence Motives (Brief):** a measure of tobacco dependence.

Study Synopsis

Study Design: Randomized, double-blind (cigarette nicotine content), multi-center study that will examine the impact of cigarette nicotine content, e-liquid (vaping device) nicotine content and e-liquid flavor choices on smoking behavior.

Primary Aim: To evaluate the impact of very low nicotine content (VLNC) cigarettes, e-liquid nicotine content, and e-liquid flavoring on the total number of cigarettes (combined study plus non-study). The hypothesis is that relative to normal nicotine content (NNC) cigarettes, VLNC cigarettes will reduce cigarettes smoked as well as reduce cigarette dependence, reduce exposure to toxicants, increase use of the vaping device and increase abstinence from cigarettes. These differences between VLNC and NNC cigarettes will be greater when participants are provided e-liquids with higher nicotine concentration and a choice of both tobacco and non-tobacco flavors.

Secondary Aim: To test the impact of nicotine content in cigarettes, nicotine concentration of e-liquids, and access to non-tobacco flavors of e-liquids on subjective effects. The hypothesis is that relative to NNC, VLNC cigarettes will decrease the positive effects of smoking and increase withdrawal. Conversely, vaping will produce more positive effects and withdrawal relief in participants assigned to VLNC vs. NNC cigarettes. These differences in the effects of vaping (between participants assigned VLNC vs. NNC cigarettes) will be greater when e-liquids a) are available in both tobacco and non-tobacco flavors (positive effects); and b) when e-liquids have 1.8% vs. 0.3% nicotine (positive effects and withdrawal relief).

Population: Cigarette smokers not intending to quit, who have also tried vaping.

Study Procedures: Subjects will undergo one week of monitoring of usual brand cigarette smoking. They will then be randomly assigned to one of eight experimental groups (2x2x2 design) receiving: study cigarettes with low versus normal levels of nicotine; e-liquids with 0.3% versus 1.8% nicotine content; and choice of e-liquid flavors described as tobacco versus tobacco and non-tobacco flavors. All subjects will be able to use these products for a period of 12 weeks. Both subjects and study staff will be blind to the nicotine content of the cigarette; e-liquid nicotine content and flavor will be open label. After the 12-week experimental phase, there will be a final, 30-day follow-up visit.

Accrual Goal: 480; 60 people in each of the 8 experimental conditions

Enrollment Goals Per Site: August, 2018 – August, 2021: 7 randomized per month

1. Background

1.1. Tobacco Regulation

Over 44 million people in the United States (Centers for Disease Control and Prevention, 2002) and 1.2 billion worldwide smoke cigarettes (2014; Shafey & American Cancer Society, 2009). With 480,000 deaths per year in the US and 6 million per year world-wide with speculations of 7 million deaths per year if current trends in smoking continue through 2020 (Shafey & American Cancer Society, 2009), it is critical to have strong tobacco control policies in place to minimize the casualties from tobacco use.

According to Orleans and Slade (1993) and Giovino (2002), there are four main targets for tobacco control: the Agent, the Vector, the Host and the Environment. Most recent tobacco control efforts have been aimed at the Host (tobacco prevention and cessation programs), the Environment (policies such as smoking bans, increased taxes, anti-smoking media campaigns, advertisement bans, pictorial warning labels) and the Vector (tobacco law suits). Relatively little attention has been focused on the Agent (the tobacco product). Altering tobacco products in ways to reduce mortality and morbidity that complement current tobacco control measures may be an important next step in tobacco control.

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) passed in 2009 provides the FDA with the authority to regulate tobacco products. One provision in this legislative act empowers the FDA to set limits on constituents in tobacco products, including nicotine if the nicotine levels are not reduced to zero. Such a measure has the potential to reduce the chance of individuals experimenting with smoking from becoming dependent and enable current smokers to quit when they are motivated to do so. Although the proposal to reduce nicotine in cigarettes has been met with skepticism by some because of concerns over compensatory smoking behavior and the potential emergence of a black market (Jarvis & Bates, 1999; Kozlowski, 2015, 2016, 2017; Shatenstein, 1999), this policy measure was considered to be technically feasible by the American Medical Association and the British Medical Association (Henningfield et al., 1998), by tobacco control researchers, policymakers and governmental officials who were convened in a meeting on nicotine regulation (Hatsukami, Perkins, et al., 2010), and by the WHO Study Group on Tobacco Product Regulation (TobReg, 2015). Most importantly, in July 2017, FDA Commissioner Gottlieb announced he was “directing our Center for Tobacco Products to develop a comprehensive nicotine regulatory plan premised on the need to confront and alter cigarette addiction.” This announcement was followed on March 16, 2018 by the release of the Advance Notice of Proposed Rulemaking entitled “Tobacco Product Standard for Nicotine Level of Combusted Cigarettes” (ID: FDA-2017-N-6189-0001) “to obtain information for consideration in developing a tobacco product standard to set the maximum nicotine level for cigarettes.”

1.2. Effects of Very Low Nicotine Content Cigarettes

Studies of very low nicotine content cigarettes (VLNC; e.g., <2.4 mg/g) suggest that, acutely, they produce many effects in smokers that are qualitatively similar to normal nicotine content (NNC; e.g., 15.8 mg/g) cigarettes, but with somewhat reduced efficacy. VLNC cigarettes reinforce behavior

(Shahan et al., 1999; Shahan et al., 2001), maintaining similar rates of self-administration as NNC cigarettes in brief sessions even though participants prefer NNC cigarettes when given a choice (Shahan et al., 1999). Compared to not smoking, VLNC cigarettes increase ratings of satisfaction and liking (Donny et al., 2007; Donny & Jones, 2009; Rose et al., 2000), although the magnitude of these effects is typically reduced compared to those produced by NNC cigarettes (Butschky et al., 1995; Gross et al., 1997; Robinson et al., 2000). VLNC cigarettes also reduce withdrawal and craving (Pickworth et al., 1999), although some symptoms (e.g., restlessness, impatience) may be more effectively alleviated by NNC cigarettes (Buchhalter et al., 2005).

Studies in which VLNC cigarettes were utilized over a longer period suggest potential benefits in terms of reduced smoking. When only VLNC cigarettes were available in an inpatient setting, the number of cigarettes smoked and the motivation to smoke during periods of abstinence decreased over time (Donny et al., 2007). Longer, outpatient studies have either found no change in smoking rates (Benowitz et al., 2007; Benowitz et al., 2009; Benowitz et al., 2012; Donny & Jones, 2009), or a significant decline in smoking rates (Donny et al., 2015; Hatsukami et al., 2010). Some studies have also shown that VLNC cigarettes reduce nicotine dependence (Hatsukami et al., 2010) and increase quit attempts (Donny et al., 2015). In one study conducted among individuals interested in quitting smoking, there was a significant increase in smoking cessation (Hatsukami et al., 2010).

There is very little evidence of adverse outcomes associated with VLNC use, including compensatory smoking. As noted above, data available to date indicate that the number of cigarettes smoked per day tends to decrease, not increase, over time (Donny et al., 2015; Donny & Jones, 2009; Hatsukami, Kotlyar, et al., 2010). Furthermore, participants tend to reduce the volume of smoke inhaled and some studies have reported significant decreases in expired carbon monoxide (CO) (Donny & Jones, 2009; Hatsukami et al., 2010). If compensatory smoking occurs, it appears to be short-lived (Macqueen et al., 2012; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007) and may be more likely in heavily dependent smokers (Bandiera et al., 2015). Likewise, few other unintended consequences have been identified. In our recent clinical trial, there was also no evidence of an increase in depressive symptoms among those with higher depression scores at baseline (Tidey et al., 2017) and no evidence of an increase in alcohol or marijuana use (Dermody et al., 2016; Pacek et al., 2016). However, individuals who were compliant with the VLNC cigarettes did gain weight over a six-week intervention period at a rate similar to what might be expected during smoking cessation (Rupprecht et al., 2016).

Most studies to date provide smokers with only two options: smoke free study cigarettes or abstain from using tobacco, with clear instructions to not use non-study products. In this context, most smokers not only continue to smoke, but, despite instructions to the contrary, continue to use non-study cigarettes. Based on self-report, more than 75% of participants assigned to VLNC cigarettes use at least one non-study (normal nicotine) cigarette during trials that last 6 weeks or longer, typically smoking 2-4 non-study cigarettes on at least a third of the days (Benowitz et al., 2015; Donny et al., 2015). Consequently, nicotine exposure (as measured by urine total nicotine equivalents) only decreases by about 60% compared to the 97% reduction of nicotine content in the product (Donny et al., 2015). This pervasive noncompliance may attenuate the effects of VLNC cigarettes on abstinence (Dermody, Donny, Hertsgaard, & Hatsukami, 2015), but it also likely foreshadows how patterns of product use would evolve if nicotine product standards were enacted

for combusted tobacco. Some may seek out black market cigarettes or tamper with cigarettes to increase nicotine delivery, but many others may turn to easily accessible alternative products.

1.3. Very Low Nicotine Content Cigarettes and Vaping Devices

Vaping devices (e.g., e-cigarettes, vape pens, mods) use liquid that often contains nicotine, as well as varying compositions of flavorings, propylene glycol, glycerin, and other ingredients. The liquid is heated into an aerosol that the user inhales. Vaping devices have rapidly emerged as a commonly used non-combusted product in the U.S. (Agaku et al., 2014; Arrazola et al., 2015) with a rule by FDA that they be deemed a “tobacco product” ("Deeming tobacco products to subject to the federal Food, Drug, and Cosmetic Act, as amended by the Family Smoking Prevention and Tobacco Control Act," 2016) with premarket review of products required as of August, 2022. Our preliminary study suggests that approximately half of all smokers switched to VLNC cigarettes will try vaping devices when provided the opportunity (far more than any other non-combusted tobacco product; Hatsukami et al., 2017). Interestingly, there was a negative association between smoking VLNC cigarettes and use of alternative products which is consistent with evidence that vaping devices can function as a substitute for conventional cigarettes (Polosa, 2015). However, we know little about how the characteristics of vaping devices impact VLNC use and, conversely, how nicotine reduction in cigarettes impacts the use of vaping devices with different characteristics. Both nicotine and non-nicotine factors may be important. This gap is important given FDA’s intention “to address the issue of flavored tobacco products” while “not altering the nicotine content of noncombustible products such as e-cigarettes” (Gottlieb, July 28, 2017)

1.3.1. Nicotine

Nicotine delivered via vaping devices may serve a variety of functions that support its actions as a reinforcer and an appealing alternative to smoking VLNC cigarettes. Some vaping devices can deliver as much or more (among experienced users) nicotine as a traditional cigarette with a relatively rapid rate of absorption (Tmax ≤ 5 min) (Spindle, Breland, Karaoghlanian, Shihadeh, & Eissenberg, 2015). In devices similar to the one proposed here, e-liquids with 18-36 mg/ml produce cigarette-like increases in plasma nicotine concentrations after 10 puffs while lower nicotine content e-liquids produce smaller and short-lived increases in plasma nicotine (Lopez et al., 2016; Hiler et al., 2017). This pharmacokinetic profile suggests that vaping devices may have greater positive reinforcing effects than VLNC cigarettes (Ramoa et al., 2016). Vaping devices can also be used throughout the day to maintain nicotine levels that would otherwise fall by 95% or more if smokers use only VLNC cigarettes (Denlinger et al., 2016). Indeed, vaping devices reduce withdrawal symptoms in cigarette smokers (Dawkins, Turner, & Crowe, 2013; Dawkins, Turner, Hasna, & Soar, 2012), and this suppression is dependent on the nicotine concentration of the e-liquid (Dawkins et al., 2012). Relatedly, greater nicotine delivery may also result in increased risk of dependence on vaping devices (Etter & Eissenberg, 2015). Finally, nicotine also acts peripherally on receptors in the oropharyngeal cavity which may contribute to sensory effects (discussed below) that might generalize across products. Together, these data suggest that vaping devices that effectively deliver nicotine may be more likely to function as both positive and negative reinforcers and more able to compete with the reduced reinforcing effects of VLNC cigarettes.

1.3.2. Non-nicotine factors

Vaping devices have a somewhat unique feature relative to other alternative nicotine delivery systems such as the patch or gum – they can provide sensorimotor stimuli similar to combusted cigarettes, including a smoke-like vapor and a tobacco-like flavor. Decades of research highlight the importance of sensorimotor stimuli in maintaining behavior even when nicotine is absent (Caggiula et al., 2001; Rose, 2006). Stimuli associated with nicotine can elicit craving (Baker, 2015), increase the probability of use (Thornley et al., 2009), increase positive subjective experiences (Furlow, 2015; Glover & McRobbie, 2015; McNeill et al., 2015; McRobbie et al., 2015), reduce withdrawal (Hajek et al., 2015; Kalousova, 2015; McRobbie et al., 2015), and support behavior even in the absence of the drug (McRobbie, Bullen, Hartmann-Boyce, & Hajek, 2014; McRobbie et al., 2010). These data suggest that the sensorimotor experience is an important determinant of whether a product will substitute for traditional cigarettes. Vaping devices may serve this function better than other alternative products which might explain both why they were chosen most often in our pilot study (Hatsukami et al., 2017) and why they attenuate withdrawal in cigarette users even if they do not deliver nicotine (Vansickel, Cobb, Weaver, & Eissenberg, 2010).

Vaping device e-liquids are also available in a variety of non-tobacco flavors that may impact the appeal and reinforcing effects of the product. The full impact of flavors on vaping devices use is still unknown, but it seems likely that the availability of non-tobacco flavors influences the likelihood of use. Recent estimates are that 53% of adults use vaping devices with flavors other than tobacco (Yingst et al., 2015). Other studies also supported this assumption, demonstrating that liquid flavor choices influence appeal and choice of vaping device (Shiffman, Sembower, Pillitteri, Gerlach, & Gitchell, 2015; Yingst et al., 2015). If flavors impact the appeal of vaping devices, they may also impact the likelihood that smokers will switch from VLNC cigarettes to these products.

2. Study Plan and Procedures

2.1. Study Design

480 smokers will receive Spectrum cigarettes, a vaping device (Halo Triton 650 mAh and 2.4 ml tank with a 2.2-2.4 ohm coil), and an adequate supply of e-liquid for twelve weeks. After a screening visit, when eligibility is confirmed, participants will complete a baseline session where they will be provided with their usual brand of cigarettes to smoke for one week. Participants will then complete a randomization visit in which they are randomized into one of eight groups. Participants will either receive VLNC or NNC Spectrum cigarettes (double blind), e-liquid that is either low nicotine (0.3 % or 3 mg/ml) or contains a moderate level of nicotine (1.8% or 18 mg/ml), and will choose up to three flavors – either from a selection of flavors characterized as similar to tobacco, or from a selection of flavors characterized as similar to tobacco as well as other non-tobacco flavors (e.g., blueberry). Over 12 weeks of the experimental phase, they will use these products ad libitum attending weekly laboratory visits for the first four weeks and biweekly visits from Week 6 to 12. At Week 12, participants will be required to return their study products. Participants can quit smoking or vaping

at any time during the study; if participants are interested in quitting they will be provided appropriate resources. Approximately 30 days after the week 12 visit, they will return to the lab for a follow up visit to assess smoking behavior and biomarkers of exposure.

Estimated Timeline (may vary)	In person sessions	Cigarette provided	END provided
0 days	Screening		
7 days	Baseline	Usual brand	
14 days	Randomization	Study cigarette	Study END
21 days	Week 1	Study cigarette	Study END
28 days	Week 2	Study cigarette	Study END
35 days	Week 3	Study cigarette	Study END
42 days	Week 4	Study cigarette	Study END
56 days	Week 6	Study cigarette	Study END
70 days	Week 8	Study cigarette	Study END
84 days	Week 10	Study cigarette	Study END
98 days	Week 12		
128 days	30-day follow-up		

2.2. Pilot

Up to four subjects (only at the Wake Forest site) will complete an abbreviated pilot procedure before implementing the full protocol for the purpose of staff training and evaluating the planned procedures. Interested participants will be recruited (as described in Section 3.1) and consented with a pilot-study specific consent form (as described in Section 3.2). Up to 12 participants will be screened (as described in Sections 3.3-3.6) and enrolled to achieve four completers. Stratification variables outlined in Section 3.7 will not be implemented. Investigational cigarettes (i.e., Spectrum) will not be used; usual brand cigarettes will be used in their place. The vaping device (Halo Triton 650 mAh and 2.4 ml tank with a 2.2-2.4 ohm coil) and e-liquids will be as proposed in the main protocol. One week after the screening visit, eligible participants will complete the "Randomization Visit" (described in Section 5) in which they will be assigned one of the four e-liquid conditions (described in Section 2.3.2) in the following order (note: assignment of pilot subjects is not random): 1) e-liquid that is low nicotine (0.3 % or 3 mg/ml) and available only in tobacco flavors; 2) e-liquid

that is moderate nicotine (1.8 % or 18 mg/ml) and available only in tobacco flavors; 3) e-liquid that is low nicotine (0.3 % or 3 mg/ml) and available in tobacco and non-tobacco flavors; 4) e-liquid that is moderate nicotine (1.8 % or 18 mg/ml) and available in tobacco and non-tobacco flavors. The pilot procedure experimental phase will last 2 weeks. After 1 week, participants will complete what is described in this protocol as the "Week 3 visit" and after 2 weeks participants will complete what is described in this protocol as the "Week 12 visit." At the last experimental lab visit, participants will be required to return their study products. The 30-day follow-up visit will not be conducted. Participants can quit smoking or vaping at any time during the pilot; if participants are interested in quitting they will be provided appropriate resources. Compensation will be provided as outlined in Section 13 with session earning up to $150 and incentives up to $70 plus $10 per visit for transportation costs ($45 for IVR calls; $25 retention bonus for completing all sessions; no incentives for compliance will be available). The potential risks are as outlines in Section 15 except for the following omissions related to the fact that usual brand cigarettes will be used: #4 and 8.

Pilot Timeline

Estimated Timeline (may vary)	In person sessions	Cigarette provided	END provided
0 days	Screening		
7 days	Randomization	Usual brand	Study END
14 days	Week 1	Usual brand	Study END
21 days	Week 2	Usual Brand	Study END

2.3 Study Products

2.3.1 Investigational Cigarettes

The National Institute on Drug Abuse has made available investigational cigarettes that vary in nicotine content for research purposes (NOT-DA-14-004). We have used these cigarettes in previous studies (e.g., Donny et al., 2015). The specific products and nicotine/tar yields are reported below. All products are manufactured by 22nd Century and distributed by the Research Triangle Institute (RTI) for NIDA. The NNC cigarettes contain approximately 15.8 mg nicotine per g of tobacco. The VLNC cigarettes contain approximately 0.4 mg nicotine per g of tobacco. Additional information including machine generated nicotine and tar yields is provided below and detailed product information including storage requirements can be found in the Investigator Brochure.

Spectrum Cigarettes to be used in this project

Condition	TPMF Code	Type*	Specifications Nicotine Yield	Specifications Tar Yield	Specification Range for Nicotine Yield
NNC	NRC600	CN	0.8 ± 0.15	10.5 ± 1.5	0.65 - 0.95
NNC	NRC601	CN-Men	0.8 ± 0.15	10.5 ± 1.5	0.65 - 0.95
VLNC	NRC102	RN	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04
VLNC	NRC103	RN-Men	0.03 ± 0.01	9 ± 1.5	0.02 - 0.04

*Legend:	
RN	Reduced Nicotine
RN-Men	Reduced Nicotine-Menthol
CN	Conventional Nicotine
CN-Men	Conventional Nicotine-Menthol

2.3.2 Vaping Devices

All participants will receive identical vaping devices – the Halo Triton (3.7 V battery; 650 mAh) and compatible Triton 2.4 ml refillable tank with 2.2-2.4 ohm coil. Participants will be instructed on how to fill them with their assigned e-liquid by study staff, and will refill them as needed during the trial. All e-liquid will be purchased from Syndicate Distribution (previously known as Nicopure Labs) with a base of 70% propylene glycol and 30% vegetable glycerin. Nicotine concentration will be either (0.3 % or 3 mg/ml) or (1.8% or 18 mg/ml), depending on randomization group (open-label). E-liquids will be stored at room temperature and protected from sustained direct light. Participants will either choose between tobacco flavors only or between tobacco flavors and additional non-tobacco flavors (open label). Participants will take home three 10-ml bottles of e-liquid solution each week (six 10-ml bottles for bi-weekly visits), and will choose up to three flavors from a menu of e-liquid choices. Tobacco flavor choices include: a “robust” tobacco flavor, a “light” tobacco flavor, and a tobacco-menthol combination flavor. Non-tobacco flavors include: three fruit flavors (berry, blueberry, watermelon), three dessert flavors (cookies and crème, chocolate, caramel), and three mint flavors (peppermint, spearmint and menthol). The device, tank, coils, and liquids were commercially available in the U.S. prior to August 8, 2016 (i.e., deeming date) and are therefore appropriate for use in this project. The nicotine of the e-liquids will be characterized prior to the start of the study and at least annually thereafter by the University of Minnesota, CENIC Biostatistics Core.

3. Screening/Baseline Visit

3.1. Recruitment

Participants will be recruited from two sites: Wake Forest School of Medicine (Site PI: Donny) and the University of Pennsylvania (Site PI: Strasser). Participants will be recruited through flyers, direct mailings, television, radio, newspaper, bus, social media, online via our recruitment website, the CTSI Registry, and Craigslist advertisements that read, "If you smoke, we could use your help. If you're (age 18-24 or 25 or older), smoke and have tried e-cigarettes or vaping multiple times, you may be eligible for a 4 month study on tobacco use—during which you will be paid for your time and effort. This is NOT intended as a treatment for smoking." Additional ads will be run as needed targeting smokers who would fit under-enrolled age categories. These ads will be identical but specify the age range ("age 18-24…" "age 25 or older…"). Individuals who are interested will leave their contact information on a voicemail, or enter it on a form on our website. Research staff will call each participant and read a script briefly explaining the study. After verbal informed consent is received, the participants will be asked questions over the phone to determine initial eligibility. If eligible and interested, they will be scheduled for an informational session during which they will be provided with a copy of the consent document and shown a PowerPoint presentation that outlines the procedures, benefits/risks, compensation and the participants' rights. They will also be able to ask questions about the study. They will receive $10 in transportation costs for the informational session. If they are still interested in participation, then they will be scheduled for an in-person screening visit. Potential participants will be instructed to bring a pack of their usual brand cigarettes, all prescription medications they are currently taking, and a valid, state-issued photo ID to the screening visit. Acceptable forms of identification include a Driver's License, State Photo ID Card, State Voter ID Card, Passport, or Military ID. If the potential participant does not have a valid, state issued photo ID, the interviewer can provide him/her with information on obtaining one. Participants will be given the option to receive study information and visit reminders by phone, email, and text message.

A participant must complete his/her in-person screening session within 30 days of completing the telephone recruitment questionnaire. If the participant is not able to attend the in-person screening visit in that timeframe, he/she will need to complete the telephone recruitment questionnaire again and will be given a new REDCap ID number.

3.2. Informed Consent Process

Before beginning the informed consent process, participants will need to produce valid, state issued photo identification. The interviewer will confirm the age and identity of the participant. If the participant is not age 18 or older, he/she will be dismissed without payment. During the in-person screening session, study information will be presented and written, informed consent will be required to participate in the screening. To ensure adequate informed consent, participants will be asked to read the first several lines aloud (to determine literacy) and will then be given ample time to read the consent document. If the interviewer determines that the participant is not literate, he/she will dismiss the person from the study. The interviewer will review the PowerPoint presentation if necessary. The participant will be instructed to read several open-ended questions aloud and

discuss the answers with the researcher. Only after the participant and the researcher are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and his/her rights as a research participant will the consent form be signed and the participant undergo screening procedures.

3.3. Screening Procedures

Physiological measures collected and recorded on paper, and entered into REDCap by the interviewer at the end of the visit:

1. Breath alcohol concentration (BrAC)
2. Expired breath carbon monoxide (CO).
3. Urinary cotinine strips, if needed
4. A urine toxicological screen
5. Weight and height
6. Pregnancy Tests (HCG detection)
7. Blood pressure and heart rate

Screening questionnaires administered on paper and entered into the study databases at the end of the visit:

1. Identifying Information Form
2. Brief Medical History Questionnaire
3. Prime MD

Screening assessments administered via interview and entered into REDCap by the interviewer:

1. Concomitant Medications Form
2. The Mini International Neuropsychiatric Interview (MINI) suicide subscale
3. Tobacco Use History Questionnaire
4. Smoking Cessation Therapy Use Questionnaire
5. Drug Use Questionnaire (12 month and 1 month version)

Assessments administered on paper and kept as a source document only:

1. Brief Medical History Follow-Up Questionnaire, if needed
2. BDI, if needed
3. GAD 2 week monitoring, if needed

Screening assessments administered directly via Redcap:

1. Demographic Questionnaire
2. Center for Epidemiological Studies-Depression Scale
3. Alcohol Use Questionnaire (12 month and 1 month version)
4. Smoking Stages of Change

If the Redcap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Redcap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

The following task will be completed after initial eligibility determination by the research assistant (prior to review by medical staff):

1. Puff topography entails having participants smoke through a device that more precisely measures puffing behavior (e.g., puff volume). At screening, participants will smoke a usual brand cigarette through the topography device.

3.4. Eligibility Determination

Research staff will determine initial eligibility after reviewing all eligibility criteria except for the medical/psychiatric history. If the participant is deemed eligible, he/she will complete the puff topography assessment, be trained on using the IVR system (see Section 9), and be scheduled to come in for the baseline visit. Participants will be instructed to use tobacco products as usual between the screening visit and the baseline visit.

Final eligibility of the participant will be determined by a licensed medical monitor (LMM) after reviewing the Brief Medical History Questionnaire, Medical History Follow-Up Questionnaire and the MINI suicide subscale. If the participant's score on the Prime MD indicates a psychiatric disorder, then the Prime MD will be submitted to the licensed medical monitor for review as well. Additionally, if the participant's score on the Prime MD indicates Major Depressive Disorder, then the Prime MD along with the Beck Depression Inventory will be submitted for review. The LMM will sign off prior to the Baseline Visit that the participant is medically stable to receive the study product(s). The LMM will not review the medical history forms of participants who are not eligible for other, non-medical reasons.

Once all the screening procedures have been completed, researchers will pay ineligible participants $30 for their time as long as they pass the drug and breathe alcohol tests and meet the minimum requirements for carbon monoxide or urinary cotinine levels. Those participants who do not pass these tests or meet these requirements will be dismissed from the study without payment. If a participant does not pass the drug test but has a current, valid prescription that would explain the failed test, then he/she will not be automatically excluded and will still receive $30.

At the end of the Screening/Baseline Visit, the researcher will complete the End of Visit Evaluation Form, which will be entered into REDCap. This will allow the researcher to make note of any

problems encountered during the visit and to assess the truthfulness of the participant regarding self-report of tobacco use.

3.5. Inclusion Criteria:

1. Age 18+
2. Daily smokers who smoke an average of at least five and 50 or fewer cigarettes per day for the last month.
3. Must have used a vaping device on 2 or more separate occasions before participating in the trial
4. Expired breath carbon monoxide (CO) level to assess recent smoking. Carbon monoxide level must be ≥ 10 ppm to confirm regular daily smoking. If CO is <10 ppm, NicAlert strips will be used to assess urinary cotinine quantity to confirm smoking status. A result of 2,000 ng/mL is needed to verify regular daily smoking.

3.6. Exclusion Criteria:

1. Unwilling to use research cigarettes or a vaping device as part of the trial
2. Currently trying to quit or intending to quit smoking in the next 60 days
3. Currently seeking treatment for smoking cessation
4. A quit attempt in the past 30 days resulting in greater than 3 days of abstinence
5. Using tobacco products, including nicotine replacement therapies or other pharmacotherapies (other than cigarettes, vaping devices or roll-your-own tobacco) more than 9 days in the past 30 days
6. Roll your own tobacco users that are unwilling to smoke machine manufactured cigarettes as part of the trial
7. Use of vaping devices > 15 days of the last 30
8. Conditions in which participation is likely to pose a significant threat to health or for which the condition could interfere with the ability of the participant to fully participate
9. Significant unstable medical conditions (any significant **change** in a serious medical condition occurring during the past 3 months including cardiovascular disease, COPD, and cancer, as determined by the licensed medical monitor)
10. Significant unstable psychiatric conditions (any significant **change** in psychiatric symptoms during the past 3 months as determined by the licensed medical monitor)
11. Schizophrenia and schizoaffective disorder
12. Positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, and PCP. Positive test for marijuana only allowed. Failing temperature strip for the sample or unable to provide enough urine sample for the drug screen.
    a. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone (clinic letter) will not be excluded.
13. Self-reported illicit use of any drug including marijuana ≥ 10 days in the past month
14. Breath alcohol level > 0.01 (g/dL), as measured by a breath sample.
15. Binge drinking alcohol (more than 9 days in the past 30 days, 4/5 drinks in a 2-hour period (female/male))

16. Pregnant, trying to become pregnant or breastfeeding
17. Failure to agree to use adequate protection to avoid becoming pregnant during the study
18. Currently taking any one of the following medications:
    a. Phenytoin [Brand Name: Dilantin]
    b. Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]
    c. Oxcarbazepine [Brand Name: Trileptal]
    d. Primidone [Brand Name: Mysoline]
    e. Phenobarbital
    f. Bendamustine [Brand Name: Treanda]
    g. Clopidogrel [Brand Name: Plavix]
    h. Clozapine [Brand Name: Clozaril, FazaClo]
    i. Erlotinib [Brand Name: Tarceva]
    j. Flecainide [Brand Name: Tambocor]
    k. Fluvoxamine [Brand Name: Luvox]
    l. Irinotecan [Brand Name: Camptosar]
    m. Olanzapine [Brand Name: Zyprexa]
    n. Tacrine [Brand Name: Cognex]
    o. Theophylline [Brand Name: Theo Dur]
19. CO reading >80 ppm
20. Systolic BP greater than or equal to 160 mm/Hg
    a. Participants failing for blood pressure will be allowed to re-screen once.
21. Diastolic BP greater than or equal to 100 mm/Hg
    a. Participants failing for blood pressure will be allowed to re-screen once.
22. Systolic BP below 90 mm/Hg
    a. Participants failing for blood pressure will be allowed to re-screen once.
23. Diastolic BP below 50 mm/Hg
    a. Participants failing for blood pressure will be allowed to re-screen once.
24. Heart rate greater than or equal to 105 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.
25. Heart rate lower than 45 bpm
    a. Participants failing for heart rate will be allowed to re-screen once.
26. Indicating any suicidal ideation in the past month or suicide attempts in the past 5 years (if within the past 6-10 years, LMM approval required).
27. Inability to independently read and comprehend the consent form and other written study materials and measures.
28. Having participated in a research study during the past three months in which the participant:
    a. Smoked a cigarette that was not his/her usual brand cigarette for more than one day
    b. Used any tobacco products beyond normal use for more than one day
    c. Used any nicotine replacement products or smoking cessation medications for more than one day
29. Having participated in prior studies involving reduced nicotine cigarettes in the past three years.
30. Household member enrolled in the study concurrently
31. Self-reported allergies to propylene glycol and/or vegetable glycerin.

32. Previous adverse reactions when using vaping devices.

Children under age 18 are excluded because they cannot legally buy cigarettes. Those with unstable medical or psychiatric conditions are excluded as these symptoms could affect a participant's ability to complete the study. Examples include but are not limited to the following: angina, stroke, heart attack which occurred since phone screening, blood clots in the arms or legs for which the individual is undergoing active medical treatment, cancer requiring active chemotherapy or radiation therapy, severe shortness of breath caused by conditions such as uncontrolled asthma, COPD, or arrhythmia, active untreated infection such as pneumonia, active untreated endocrine disorder such as hyperthyroidism. The LMM can also exclude participants for conditions in which participation is likely to pose a significant threat to health or for which the condition could interfere with the ability of the participant to fully participate (e.g. severe allergic reaction to propylene glycol or vegetable glycerin found in e-liquids). We will exclude those currently seeking smoking treatment, those who have quit smoking for longer than 3 days in the past 30 days or are planning to quit in the next 60 days, as participation in this study may not lead to reductions in smoking. We will exclude pregnant and nursing women and anyone with current or recent alcohol or drug abuse problems as these factors could independently affect smoking behavior during the study. Individuals with baseline CO readings greater than 80 ppm, those with heart rate or blood pressure readings that are out of range and anyone who has attempted suicide in the past five years will be excluded from the study for safety concerns. Participants currently prescribed one of the medications listed will be excluded because this medication could interfere with the biomarkers or possibly cause an adverse smoking-drug interaction if there are changes in smoking behavior. If an individual has recently participated in a smoking research study that changed his/her smoking behavior, this person would be excluded because he/she would not have a stable smoking baseline. Because participants are required to complete portions of the protocol independently both in the lab and at home, they will need to be able to independently read and comprehend the study materials. Multiple participants within the same household may not enroll concurrently to avoid product exchanging. Very frequent use of vaping devices is exclusionary to target individuals who are primarily cigarette smokers and to decrease the likelihood that a participant will have a vaping device they find more satisfying than the study vaping device. However, individuals must have at least tried vaping devices at least on 2 separate occasions, without an allergic or otherwise adverse experience, to maximize the likelihood that participants will try the vaping device provided to them.

3.7. Stratification

Throughout the study, we will stratify by menthol status (no required sample size) and age range (no required sample size 18-24/25+). We recognize that it will likely be more challenging to recruit young adults. We will make use of targeted recruitment strategies (e.g., social media for the recruitment of young adults).

4. Baseline Visit

4.1. Baseline Visit Scheduling Requirements

Participants will return for a baseline visit one week after their screening visit. The ideal visit window is 6-10 days, but could be extended to as many as 21 days if necessary. If the participant is unable to attend the baseline visit within 21-days, they will not be eligible to continue. At this visit they will complete a variety of assessments and will be provided with a 14-day supply of their usual brand cigarette to smoke between the baseline visit and the randomization visit.

4.2. Baseline Visit Procedures

Physiological measures collected and recorded on paper, and entered into REDCap at the end of the visit:

1. BrAC
2. Weight
3. CO
4. Blood Pressure (lab visit & Product evaluation)
5. Heart Rate (lab visit & Product evaluation)

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1. Saliva sample:
   Participants will be asked to provide two saliva samples during the Baseline Visit for assessment of nicotine metabolite ratio (NMR), an indicator of CYP2A6 enzyme activity. Participants must wait 30 minutes after arrival to the lab before collecting the first saliva sample. During this time, participants cannot eat, drink, chew gum or use tobacco/nicotine products. After collecting the sample, the participant is provided time to eat and/or drink and must wait another 30 minutes before collecting the second saliva sample. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Saliva samples will be sent regularly to be analyzed and stored at the University of Minnesota.

2. First void urine sample for smoking biomarker assessment**:**
   Participants will be asked to bring a urine sample (first void of the day) to the Randomization Visit for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota. We will assess mercapturic acids (markers of exposure to volatile organic compounds) and total nicotine equivalents (TNEs; a measure of nicotine exposure). If a participant forgets to bring his/her urine sample, then the spot urine sample will be used.

3. Spot urine sample for assessing baseline anatabine:
   Participants will be asked to provide a urine sample in the lab for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed for anatabine (a non-nicotine

tobacco alkaloid present in high levels in NNC and commercial but not VLNC cigarettes) and stored at the University of Minnesota.

Assessments administered via interview and entered into REDCap by the interviewer:

1. Concomitant Medications Form
2. Adverse Event Form, if needed
3. Health Changes Questionnaire
4. IVR Review of Daily Call and follow-up on missing and unusual reports and Timeline Follow-back Questionnaire (since last visit); if needed
5. Intention to Quit Smoking and Vaping

Assessments administered on paper and kept as a source document only:

4. BDI, if needed
5. GAD 2 week monitoring, if needed

Assessments administered directly via REDCap:

1. Environmental and Social Influences on Tobacco Use Questionnaire
2. Purchase Task: Usual Brand
3. Respiratory Health Questionnaire
4. Smoking Expectancies and Vaping Expectancies Questionnaires
5. Vaping Utility Questionnaire
6. Perceived Health Risks Questionnaire: Usual Brand

Tasks completed at baseline:

1. Product evaluation: will be assessed after participants take 4 puffs of their usual brand cigarette at baseline. Following the sampling period, participants will complete the *Cigarette Evaluation Scale* (CES), which assesses the extent to which the product they just sampled produced various subjective effects including satisfaction, good taste, dizziness, reduced appetite, nausea, and enjoyable sensations in the throat and chest on a 7 point Likert-type scale. We will also assess changes in heart rate and blood pressure related to smoking.

4.3. Distributing Usual Brand Cigarettes

Participants will receive a supply of their usual brand cigarette to smoke between the baseline visit and the randomization visit. Participants will receive a 14-day supply and be instructed to bring their entire supply (empty packs and unused cigarettes) to the randomization visit. Participants will be notified that failure to return products throughout the study will result in removal from the study.

5. Randomization Visit

5.1. Randomization Visit Scheduling Requirements

The ideal target window between the baseline and randomization visit is 6 to 10 days. However, in rare cases, the window may be extended to as many as 21 days after the baseline visit. If the visit window is extended beyond 10 days, the participant will receive a larger supply of usual brand cigarettes (see Product Distribution section). If a participant cancels and reschedules their randomization visit outside of the 10-day window, staff will encourage the participant to return to the lab for an unanticipated visit to obtain additional product. If the participant is unable to attend the randomization visit within 21-days, they will not be eligible to continue.

5.2. Experimental Conditions

During the Randomization Visit, participants (N=480; 240 per site) will be randomized equally into one of eight experimental conditions. Participants will be assigned a cigarette that matches their menthol preference. Groups will be stratified by age and menthol status with no required sample size.

	Very Low Nicotine Cigarettes (VLNC)		Normal Nicotine Cigarettes (NNC)	
Range of Flavors	**0.3% or 3mg/ml** nicotine e-liquid	**1.8% or 18 mg/ml** nicotine e-liquid	**0.3% or 3 mg/ml** nicotine e-liquid	**1.8% or 18 mg/ml** nicotine e-liquid
Tobacco Flavors	**0.3% or 3 mg/ml** nicotine e-liquid	**1.8% or 18 mg/ml** nicotine e-liquid	**0.3% or 3 mg/ml** nicotine e-liquid	**1.8% or 18 mg/ml** nicotine e-liquid

5.3. Randomization Visit Procedures

Physiological measures collected and recorded on paper, and entered into REDCap at the end of the visit:

1. BrAC
2. Weight
3. CO
4. Blood Pressure
5. Heart Rate
6. Urine Pregnancy Test, if applicable

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1. First void urine sample for smoking biomarker assessment**:**

Participants will be asked to bring a urine sample (first void of the day) to the Randomization Visit for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota. We will assess mercapturic acids, and total nicotine equivalents (TNEs). If a participant forgets to bring his/her urine sample, then the spot urine sample will be used.

2. Spot urine sample for assessing baseline anatabine:
   Participants will be asked to provide a urine sample in the lab for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota.

Assessments administered via interview and entered into REDCap by the interviewer:

1. Concomitant Medications Form
2. Adverse Event Form, if applicable
3. Health Changes Questionnaire
4. IVR Review of Daily Call and follow-up on missing and unusual reports and Timeline Follow-back Questionnaire (since last visit); if needed
5. Intention to Quit Smoking and Vaping

Assessments administered on paper and kept as a source document only:

1. BDI, if applicable
2. GAD 2 week monitoring, if needed

Assessments administered directly via REDCap:

1. Respiratory Health Questionnaire
2. Cigarette Dependence Measures
3. Vaping Device Dependence Measures
4. Minnesota Nicotine Withdrawal Scale
5. Context of Product Use-Baseline
6. Urge to Use Questionnaire-Baseline
7. Perceived Health Risks Questionnaire: Study Products

If the Redcap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Redcap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

The following tasks will be completed after participants are randomized:

1. Product evaluation will be assessed after participants take four puffs of each assigned product with a 30-second inter-puff interval, and a 15-minute inter-product interval

(Randomization, Weeks 02, 04, 08, and 12). Following each sampling period, participants will complete the *Cigarette Evaluation Scale* (CES; modified to apply to both cigarettes and vaping devices), which assesses the extent to which the product they just sampled produced various subjective effects including satisfaction, good taste, dizziness, reduced appetite, nausea, and enjoyable sensations in the throat and chest on a 7 point Likert-type scale. We will also assess changes in heart rate and blood pressure related to each product.

2. Preference Task will consist of a series of 10 choice trials, each lasting 1 minute, with a 2 minute inter-trial interval. During each trial, participants will be presented (via computer) with a choice between taking 2 puffs of the cigarette, 2 puffs of the e-cigarette, or abstaining. Indices derived from this task include: total number of cigarette puffs; total number of vaping device puffs; and total number of choices to abstain from product use.

Researchers will complete the End of Visit Evaluation Form, which will be entered into REDCap. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regard to self-report of tobacco use.

6. Experimental Phase

6.1. Study Product Distribution

The Administrative Core for the Center for the Evaluation of Nicotine in Cigarettes (CENIC) will be responsible for removing all identifying information from cigarettes received from the Research Triangle Institute (RTI), labeling each carton with a blind code, assigning product using this blind code based on the randomization schedule being provided by the CENIC Biostatistics Core, and shipping cigarettes to each site as needed based on recruitment. The site will be responsible for tracking product received and distributed to participants, collecting unused product from participants, and destroying unused open packs. The participants, investigators and study staff will not have knowledge of which product is given to a participant or whether different participants received the same or different product with regards to study cigarettes.

Between Visits 00, 01, 02, 03, and 04, participants will receive a 14-day supply of research cigarettes at each visit. Between Visits 04, 06, 08, 10, and 12, participants will receive a 28-day supply. This will ensure adequate availability of cigarettes in the numerous locations participants may typically keep a supply (home, work, vehicle, etc.) as well as avoid expending the entire supply if they miss a scheduled visit.

Additionally, participants will receive two vaping device batteries and one tank per flavor choice. Tanks are refillable, but do need to be replaced occasionally. The Administrative Core will apply a product tracking label/code to each e-liquid bottle. Product will be assigned using this code based on the randomization schedule being provided by the CENIC Biostatistics Core. Participants will receive three 10-ml e-liquid bottles at each weekly visit (Visit 00, 01, 02, 03) and six 10-ml bottles at each bi-weekly visit (Visit 04, 06, 08, 10), divided among as many as three different flavor choices. After choosing flavors, participants will fill an empty tank with each of their chosen e-liquid flavors in the lab with help of study staff. This process allows study staff to train participants on the proper

method for filling tanks. Participants will return their empty e-liquid bottles and any unused product at each weekly visit. Unopened e-liquid bottles will be considered full and all bottles with > 5 ml will be redistributed to the same participant if participants choose the same flavor in a future week. If a participant loses their vaping device or e-liquids, we will provide replacements up to two times. If a participant loses their device or liquids more than twice, we may withdraw them from the study. When participants are provided with their study vaping device for the first time, they will be told that losing their device or e-liquids multiple times may result in study withdrawal.

If there is prior knowledge a participant will be missing a visit (e.g., planned vacation, laboratory closure, etc.), or a participant is unable to attend the randomization visit within the 10-day window, then the participant will be provided with an adequate supply of study product until their next visit. The participant will be given a 21-day supply of cigarettes if they will miss Visit 01, 02 or 03 or if the randomization visit is between 11 and 17 days from screening, a 28-day supply of cigarettes if they will miss Visit 04 or the randomization visit is 18 or more days from screening, and a 35-day supply of cigarettes if they will miss Visit 06, 08 or 10. For e-liquids, participant will be given 5 bottles (10 ml each) if they will miss Visit 01, 02 or 03, 6 bottles if they will miss Visit 04, and 8 bottles if they will miss Visit 06, 08 or 10. In addition, participants can come to the laboratory during normal business hours to receive additional study product if needed.

6.2. Study Product Accountability

Participants will be required to keep track of the vaping device, tanks, and all the cigarettes and e-liquid provided to them. They will be instructed to return all unused cigarettes and empty cigarette packs and vaping device, tanks, and e-liquid bottles each week. Because participants are provided with an ample supply of research cigarettes and e-liquid (to account for unanticipated missed visits or greater than anticipated use), they will be expected to return unused product at each visit to remain enrolled in the study.

Research staff will complete the 'Product Accountability Log' directly in REDCap. Any discrepancies in the product dispensed versus product returned will be discussed and recorded in the log. Empty cigarette packs and/or empty bottles will be saved. Unused cigarettes or bottles will be redistributed to the participants during Visits 01-12. At Visit 10, participants will be made aware that they will be required to turn in all study products (cigarettes and vaping devices) at Visit 12.

During the Experimental Phase, if participants lose cigarettes or e-liquids and require an unscheduled visit to the laboratory to supplement their supply, they will be told the next time they lose their supply of either product they will have to wait until their next scheduled appointment to receive more product.

6.3. Experimental Phase Visit Scheduling Requirements

A computer-generated ideal visit calendar will automatically generate the ideal visit windows once the participant has been randomized. If a participant misses a visit and is not able to reschedule during the window, that visit will not be 'made-up' in the future. All measures that were not completed will be considered missing data and will not be collected during future visits. If a visit mistakenly occurs outside of the designated window, this is a protocol deviation. A 'Protocol Deviation Form'

will need to be completed and tracked in REDCap. If a participant is not able to attend Visit 12, then it should be rescheduled even if it is outside of the scheduling window. This will be documented as a protocol deviation. Participants that do not attend scheduled lab visits, miss daily IVR phone calls, and do not respond to phone messages will be considered lost to follow-up. A certified letter will be sent to notify them as defined by the site's Standard Operating Procedure (SOP).

6.4. Visit 01, 02, 03, 04, 06, 08, 10, and 12 Procedures

Physiological measures collected and recorded on paper, and entered into REDCap at the end of the visit:

1. BrAC
2. Weight
3. CO
4. Blood Pressure
5. Heart Rate
6. Urine toxicology assessment (Visit 12 only)
7. Pregnancy test (if applicable, Visits 4, 8, 12 only)

Biological specimens collected, stored, and entered into CENIC Biosamples Collection Platform:

1. First void urine sample for smoking biomarker assessment (Visits 4, 8, 12)**:**
   Participants will be asked to bring a urine sample (first void of the day) for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota. We will assess mercapturic acids, and total nicotine equivalents (TNEs). If a participant forgets to bring his/her urine sample, then the spot urine sample will be used.

2. Spot urine sample for assessing baseline anatabine:
   Participants will be asked to provide a urine sample in the lab for biomarker assessment. Samples will be stored at temperatures approximately at --20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota.

Assessments administered via interview and entered into REDCap by the interviewer:

1. Concomitant Medications
2. Adverse Event Form, if applicable
3. Health Changes Questionnaire
4. IVR Review of Daily Call and follow-up on missing and unusual reports and Timeline Follow-back Questionnaire; if needed
5. Intention to Quit Smoking and Vaping
6. Drug Use Questionnaire, 1 month version (Visits 4, 8, 12)

Assessments administered on paper and kept as a source document only:

1. BDI, if applicable
2. GAD 2 week monitoring, if needed

Assessments administered directly via REDCap:

1. Respiratory Health Questionnaire
2. MNWS
3. Urge to Use Questionnaire-Experimental
4. Perceived Health Risks Questionnaire: Study Products (Visits 2, 4, 8, 12)
5. CESD (Visits 4, 8, 12)
6. Alcohol Use Questionnaire, 1 month version (Visits 4, 8, 12)
7. Context of Product Use-Experimental Version (Visits 4, 8, 12)
8. Smoking Stages of Change (Visits 4, 8, 12)
9. Cigarette and Vaping Dependence Questionnaires (Visits 4, 8, 12)
10. Purchase task-Study Cigarette + Vape Version (Visit 12)
11. Smoking and Vaping Expectancies Questionnaires (Visit 12)
12. Vaping Utility Questionnaire (Visit 12)
13. Environmental Tobacco Smoke Questionnaire (Visit 12)
14. Predicted Behavior Questionnaire (Visit 12)
15. End of Study Questionnaire (Visit 12)

In the event that the Redcap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Redcap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered in to REDCap.

The following tasks will be completed:

Product evaluation will be assessed after participants take 4 puffs of each assigned product with 15-minute inter-product interval (Randomization and Visits 02, 04, 08, and 12). Following each sampling period, participants will complete the *Cigarette Evaluation Scale* (CES; modified to apply to both cigarettes and vaping devices), which assesses the extent to which the product they just sampled was produced various subjective effects including satisfaction, good taste, dizziness, reduced appetite, nausea, and enjoyable sensations in the throat and chest on a 7 point Likert-type scale. We will also assess changes in heart rate and blood pressure related to each product. The product evaluation will be omitted if the participant indicates they are currently abstaining from use of the product (Question 3 of the Intention to Quit Log).

Puff topography entails having participants puff through a device that more precisely measures puffing behavior (e.g., puff volume). At Visits 01 and 10, participants will puff both their assigned cigarette and vaping device through the topography device. Puff topography will be omitted if the participant indicates they are currently abstaining from use of the product (Question 3 of the Intention to Quit Log).

Researchers will complete the End of Visit Evaluation Form, which will be entered into REDCap, after each visit during the experimental phase. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regard to self-report of tobacco use.

6.5. Product and Procedures Compliance Review Sessions

Participants will be counseled at each visit to the lab about their use of the study products. They will be asked about any concerns or obstacles associated with using the study cigarettes and vaping device. The importance of honest self-reporting will be stressed. If difficulties are encountered, participants will be asked why they think they are experiencing difficulties (e.g., taste, withdrawal symptoms) and to problem-solve how to deal with these difficulties to meet the protocol requirements.

Additionally, participants will be counseled about IVR completion, visit attendance, task engagement and product accountability.

Preparation for Visit 12

At the end of Visit 10, participants will be reminded that the study will conclude at Visit 12 (except for the 30-day follow up visit). Further, at Visit 12 they will be expected to turn in all study tobacco products. Participants can make or schedule a quit attempt at any time throughout the study (see related procedure in Section 15: Quit Attempts), including at this time. The two-week period between Visit 10 and Visit 12 will allow participants to prepare accordingly for the end of the study or a quit attempt.

After a participant has completed all study procedures, they are required to turn in all study cigarettes, vaping devices, tanks and e-liquids.

The research assistant will read the following script to all participants at the Week 12 visit:

"Nicotine in cigarettes is very addictive and robs people the choice of being able to quit smoking or not. In addition to being in cigarettes, nicotine is in smokeless tobacco products, snus, nicotine patches, nicotine lozenges, nicotine gum, and most e-liquid for vaping devices. Among these products, cigarettes contain the most toxins and cancer-causing chemicals because they are burned and this smoke is associated with the greatest risk for disease and death. As many as half of the people who smoke cigarettes will die from smoking-related disease. The number of harmful chemicals in vaping products may be less because they are not burned. Are you interested in additional resources about vaping risks? (provide list of online resources)

There is a 50% chance that the study cigarettes provided to you during the study were very low in nicotine content. In prior studies, smokers assigned to very low nicotine cigarettes smoked less and made more quit-attempts than smokers of cigarettes with normal nicotine levels. Before you go, we want to encourage you to abstain (continue abstaining) from smoking. We can provide you with some resources that may help you quit. Would you like a copy of those resources? (provide "Clearing the Air," state Quitline number, smokefree.gov). Are you interested in quitting now or in the near future? (If yes) Do you want to take five minutes to make a personalized quit plan that we

can print off for you? (provide smokefree.gov/build-your-quit-plan-results). We also encourage you to consult with your physician and use any medications he/she deems appropriate."

7. 30 Day Follow-Up Visit

Participants will return to the lab between 25 and 35 days after Visit 12 to assess their smoking patterns. The purpose of this visit is to discuss tobacco product use since the study ended and obtain physiological measures. Additionally, any Adverse Event Forms that remain open from the last session will be discussed. If the participant became pregnant during the study, this would have been recorded as an adverse event. During this visit, the research assistant will confirm her due date. This event will remain open until delivery. At that time, the licensed medical monitor will contact the participant to ask a few questions about the baby's health and will update the Adverse Event Form.

Physiological measures collected and recorded on paper, and entered into REDCap at the end of the visit:

1. BrAC
2. Weight
3. CO
4. Blood Pressure
5. Heart Rate

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1. Spot urine sample for assessing baseline anatabine:
   Participants will be asked to provide a urine sample in the lab for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota.
2. First void urine sample for smoking biomarker assessment. Participants will be asked to bring a sample (first void urine of the day) for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be send quarterly to be analyzed and stored at the University of Minnesota. Total nicotine equivalents and mercapturic acids will be assessed. If a participant forgets to bring his/her urine sample, then the spot urine sample will be used.
3. Total nicotine equivalents at the 30-day follow-up will be compared to baseline samples. At the discretion of the PI, a letter will be sent to participants who demonstrate a 100% increase relative to baseline to alert them of their nicotine exposure, advise them to try to reduce their nicotine/tobacco use and provide cessation resources.

Assessments administered via interview and entered into REDCap by the interviewer:

1. 30-Day Tobacco Use Questionnaire
2. Concomitant Medications

3. Adverse Event Form, if needed
4. Health Changes Questionnaire
5. Drug Use Questionnaire (1-month version)

Assessments administered on paper and kept as a source document only:

1. BDI, if needed
2. GAD 2 week monitoring, if needed

Assessments administered directly via REDCap:

1. Respiratory Health Questionnaire
2. Alcohol Use Questionnaire (1-month version)
3. Cigarette Dependence Questionnaire
4. Vaping Dependence Questionnaire
5. Smoking Stages of Change

Qualitative Interview (Wake Forest Site Only) collected on paper and audio recorded:
A qualitative interview may be conducted to discuss the following topics:
1) Product Use Patterns
2) E-liquid Flavor Selection
3) Tobacco Product Non-compliance
4) General Study Feedback

In the event that the Redcap website is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's binder. The interviewer will enter the data into Redcap when it resumes functioning properly. This information should be recorded in the 'End of Visit Evaluation Form' and entered into REDCap.

Once a participant has completed all study procedures and all open events have been closed, the PI will review the participant's binder and sign a form indicating study completion for that participant.

Researchers will complete the End of Visit Evaluation Form, which will be entered into REDCap. This will allow the researcher to make note of any problems encountered during the visit and to assess the truthfulness of the participant in regard to self-report of tobacco use.

8. Procedures for Early Termination Visits and Withdrawal

8.1. Withdrawal Procedures

If the decision to withdraw a subject occurs at a study visit, regular clinic visit procedures will be conducted as well as the additional termination procedures as described in section 8.2. If it is determined via a phone call that withdrawal is appropriate or if the subject is dropping out, we will ask the subject to attend an exit visit to return study product and equipment (e.g. cell phone if

issued), complete questionnaires, product accountability and safety assessments and to receive their final study payment.

If the subject refuses an exit visit, we will request that at the minimum, study investigational products be returned and product accountability be completed. We will also stress the importance of being able to assess safety measures for the subject's safety.

8.2. Early Termination

If a participant decides to withdraw from the study prior to completion or if they are withdrawn by the PI or LMM due to safety concerns, they will be scheduled for an early termination visit. If the participant is seen within the window of a regularly scheduled visit, all measures for that visit will be collected. Additional questionnaires and safety measures may be obtained (urine sample for biomarkers and pregnancy screen, CES-D, and BDI-II if appropriate) if not scheduled during the normal visit. If the subject is seen outside of a regularly scheduled visit window, the following measures will be obtained:

Physiological measures collected and recorded on paper, and entered into REDCap at the end of the visit:

1. BrAC
2. Weight
3. CO
4. Blood Pressure
5. Heart Rate
6. Pregnancy test (if applicable)

Biological specimens collected, stored, and entered into CENIC Biosample Collection Platform:

1. Spot urine sample for assessing baseline anatabine:
   Participants will be asked to provide a urine sample in the lab for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be sent regularly to be analyzed and stored at the University of Minnesota.
4. First void urine sample for smoking biomarker assessment. Participants will be asked to bring a sample (first void urine of the day) for biomarker assessment. Samples will be stored at temperatures approximately at -20°C (UPenn) or -80°C (Wake Forest). Urine samples will be send quarterly to be analyzed and stored at the University of Minnesota. Total nicotine equivalents and mercapturic acids will be assessed. If a participant forgets to bring his/her urine sample, then the spot urine sample will be used.

Assessments administered via interview and entered into REDCap by the interviewer:

1. Concomitant Medications
2. Adverse Event Form, if applicable
3. Health Changes Questionnaire
4. IVR Review of Daily Call and follow-up on missing and unusual reports and Timeline Follow-back Questionnaire; if needed
5. Intention to Quit Smoking and Vaping
6. Drug Use Questionnaire, 1 month version

Assessments administered on paper and kept as a source document only:

1. BDI, if applicable
2. GAD 2 week monitoring, if needed

Assessments administered directly via REDCap:

The following additional assessments will be completed by all early termination participants, if not part of the usual measures scheduled for the regularly scheduled visit:

1. CESD
2. Alcohol Use Questionnaire, 1 month version
3. Environmental and Social Influences on Tobacco Use Questionnaire
4. End of Study Questionnaire

The data collected during the termination visit will be used as appropriate given the days outside of visit window, subject use of study product, measures of safety or other considerations to be determined in data analysis.

9. Assessment Descriptions

1. *Tobacco Use History and Nicotine Exposure*, derived from the Population Assessment of Tobacco and Health (PATH) allowing comparisons with a nationally representative sample of smokers measures variables such as smoking rate (current and maximum), cigarette brand, age of initiation of smoking, number of quit attempts, duration of quit attempts and duration of smoking and history of use of other tobacco and nicotine products.
2. *Demographics* asks about age and gender, race, ethnicity, current occupation and usual occupation, and income.
3. *Brief Medical History Questionnaire* to assess medical history and current health diagnoses, symptoms and past health problems including psychiatric and substance abuse and medication use.
4. *Medical History Follow-up Questionnaire* will be completed by study staff to further assess current diagnoses, symptoms or past health problems.
5. *Concomitant Medications* lists medications (prescription, over-the-counter and supplements) and doses that are taken 30 days prior and during the study.

6. *PrimeMD - Patient Health Questionnaire (PHQ),* a brief multi-choice questionnaire developed as a screening and diagnostic tool for mental health disorders of depression, anxiety, alcohol, for primary care physicians (somatoform and eating disorder questions are not used in this study).
7. *Centers for Epidemiological Studies-Depression 20-item scale* (CES-D) which measures current symptoms of depression.
8. *Mini International Neuropsychiatric Interview (MINI) suicide subscale* to evaluate suicide risk.
9. *Beck Depression Inventory 2nd Edition (BDI-II)* is a severity measure assessing symptoms of depression.
10. *Generalized Anxiety Disorder-7 (GAD-7):* measures severity of anxiety.
11. *Interactive Voice Response-Daily Call Recording System* to record amount of product use, cigarettes and other nicotine containing products on a daily basis (estimated vaping puffs per day will be recorded).
12. *IVR Review Form* will assess study and non-study use of cigarette and other products missing from the IVR calls, correct errors in IVR entries or clarify any discrepancies or unusual IVR reports. Will only be used if a correction is needed.
13. *Timeline follow back* for tobacco will only be used if a participant misses one day or more of IVR, or if an IVR correction is needed.
14. *Context of Product Use* asks what tobacco product (study cigarette, non-study cigarette, study vape, non-study vape, other products, or no products) participants are most likely to use in a variety of contextual situations.
15. *Predicted Behavior Questionnaire* questions participants about what they think their tobacco product use would look like one year from now if starting today, all cigarettes available for purchase in the United States had the same nicotine content as their assigned study cigarette.
16. *Smoking Cessation Therapy Use* captures nicotine replacement therapy use at Screening.
17. *Urge to Use Questionnaire* has participants rate their strongest urge to use a study cigarette, usual brand cigarette, and the study vaping device in the past 24 hours using a 7-point Likert scale.
18. *Cigarette/Vaping Dependence Measures* includes: Fagerstrom Test for Nicotine Dependence (FTND), Penn State Cigarette Dependence Scale, Brief Wisconsin Inventory of Smoking Motives (WISDM) primary dependence motives subscales and 3 items from PATH.
19. *Minnesota Nicotine Withdrawal Scale (MNWS)* is an 8 item assessing symptoms of tobacco withdrawal.
20. *Adverse Events* to assess the nature, severity, duration, action taken, and outcome of adverse events related to tobacco/nicotine product use.
21. *Health Changes Questionnaire* queries for any health care visits or circumstances that would indicate any change since last visits.
22. *Respiratory Health Questionnaire* rates overall health (1-10 scale) and respiratory symptoms such as cough, phlegm production, shortness of breath on a scale ranging from 0 = none up to 10 = severe with a total respiratory score determined by adding the scores of each of these items.
23. *Alcohol Use Questionnaire (1 and 12 month)* assesses frequency and quantity of alcohol use.
24. *Drug Use History (1 and 12 month)* assesses amount, frequency in past year, and past month and date of last use of illicit drugs.

25. *Perceived Health Risks* assesses perceived health risks of no tobacco use, usual brand of cigarettes and study products that are provided.
26. *Modified Cigarette Evaluation Scale and/or Product Evaluation Scale* assesses different dimensions of responses to cigarettes or other tobacco/nicotine products, (e.g., psychological reward, satisfaction, aversiveness, and additional oral and respiratory sensation items).
27. *Cigarette/Product Purchase Task* assesses demand curves of products that are chosen. This questionnaire will be used to generate demand curves by asking the subject to report the number of units of a tobacco product that they would consume in a day if the units cost various amounts of money.
28. *Smoking and Vaping Expectancy Questionnaire* to assess attitudes and beliefs about the products provided.
29. *Stages of Change* assesses the intention to quit smoking including next 30 days, 6 months and overall readiness to quit.
30. *Intention to Quit* assesses intention to quit smoking including next 30 days and 6 months and overall readiness to quit.
31. *Social and Environmental Influences on Tobacco Use* assesses tobacco/nicotine situational use and subject's opinion on potential tobacco control policies.
32. *End of Study Questionnaire,* an open-ended interview administered at follow-up which queries the subject's rationale for product selection, knowledge, attitudes and beliefs about these products, reactions to product(s) selected, reactions to a policy that reduces nicotine in cigarettes, ideas about how this policy should be conveyed to the public and what needs to be in place to reduce any negative effects.
33. *Qualitative Interview Guide* an open-ended interview administered at the 30-day Follow-Up to gather qualitative data about product use patterns, e-liquid flavor selection, non-study product use, and general study feedback. (Wake Forest Site Only)

10. Interactive Voice Response System

Participants will be trained to use the Interactive Voice Response (IVR) System, which will contact participants each day throughout the study and ask about their smoking and vaping behavior. Participants will be provided a study cell phone if they have unreliable telephone access, do not have enough monthly cell phone minutes or prefer not to use their own phone. Each day during the period between the screening visit and the Week 12 Visit the IVR system will ask participants to report their use of cigarettes, puffs of a vaping device, first tobacco product used, and minutes after waking until first tobacco product use. During each call, participants report about tobacco use during the previous calendar day (midnight to midnight), not the previous 24-hours.

The IVR system is operated by MicroAutomation, a media production company. To be enrolled in the IVR system, research staff will enter the participant's telephone number, subject identifier, and visit dates into the IVR CENIC website. Identifying information (telephone numbers) will be removed from the dataset by the biostatistics core. Please refer to MicroAutomation's privacy statement and HIPAA compliance form for additional information.

11. Study Debriefing

After data collection is complete, participants will receive a letter telling them which condition they were randomized into and the results of the study thus far.

12. Biosample Storage

The urine and saliva biosamples will be collected and stored at study sites until regular shipments to the University of Minnesota Masonic Cancer Center for analysis or long term storage. Samples that are not used for primary analysis of study biomarkers will be banked for future use related to tobacco and nicotine exposure.

13. Data Storage

Data will be stored locally at each site and at the University of Minnesota Masonic Cancer Center's Bioinformatics Core for at least 7 years after study completion.

14. Individually Identifiable Health Information

No information will be collected from medical records. Direct identifiers will be retained at each site, stored separate from all other data, and will only be available to the local study and regulatory staff. The only exception is subject telephone numbers provided to a HIPAA compliant vendor for our Interactive Voice Recording System. Other identifiable information (excluding direct identifiers) such as visit dates will be collected and accessible to study staff (i.e., a limited dataset). These variables will be removed from the final de-identified dataset by staff associated with CENIC at the University of Minnesota Biostatistics Core.

Data Collection Platforms

Data will be collected and entered into multiple platforms including the REDCap and the Interactive Voice Recording System (IVR). In the event that internet access is not functioning, the assessments will be printed out and administered on paper. The source documents will be kept in the participant's case report form binder and the interviewer will enter the data into the software when it resumes functioning properly. Biosamples will be entered into a biomarker tracking database as they are collected.

15. Participant Compensation/Incentives

Subjects will receive $30 for the Screening Visit, $20 for the Baseline and 30-day Follow-up Visits, $20 for completing each shorter visit (Week 01, 02, 03, 06, 10) and $40 for completing each longer

visit (04, 08, 12), and $60 for completing the Randomization Visit. All subjects will also receive $10 to cover transportation costs for each visit, including the informational session ($130).

In addition to compensating subjects for their time and travel, there are incentives in place to encourage retention, and compliance.

Completed IVR Calls

Participants will receive $1 for each completed IVR call. An additional bonus of $5 will be awarded for missing no calls between scheduled visits.

Retention

Those who miss no more than two visits between Visit 01 and Visit 08, and who attend both Visit 10 and 12, will receive a $100 completion bonus.

Compliance

Since we have previously observed high rates of non-compliance among those assigned to VLNC cigarettes, we think it is important to incentivize only using assigned study products. Subjects will be told that one of their spot urine samples collected between Visit 01 and Visit 12 will be randomly selected and analyzed, and if it indicates they were compliant, they will receive a $300 bonus. A missed visit will count as a non-compliant urine sample. In actuality the bonus will only be contingent on urine samples from Visit 12, but it is important for subjects to believe samples are analyzed throughout the study to encourage compliance. Since compliance cannot be assessed in participants using NNCs, all participants in those groups will receive the $300 compliance incentive unless they miss Visit 12. For those using VLNC cigarettes, the incentive will be contingent on a urinary anatabine cut-off that indicates compliance with study products. Anatabine measures will be deemed compliant at levels slightly higher (0.16 nmol/ml) than what would be expected for complete compliance (0.010 nmol/ml) to allow for variation in individual metabolism and will not penalize occasional non-study product use.

Session	Amount	Visit Distributed
Screening	$30.00	92
Baseline	$20.00	91
Randomization	$60.00	00
Short Visits (01, 02, 03, 06, 10) ($20/visit)	$100.00	01, 02, 03, 06, 10
Long Visits (04, 08, 12) ($40/visit)	$120.00	04, 08, 12
30-day follow up	$20.00	30
Travel to each visit, including the info session ($10/visit)	$130.00	Each visit
Total	**$480.00**	
Additional Incentives	**Amount**	**Visit Distributed**
IVR Calls ($1/completed call [up to $140], plus $5 bonus awarded when all calls between visits completed [up to $50])	Up to $190.00	12
Retention Bonus	$100.00	12
Compliance Bonus	$300.00	30
Total	**Up to $590.00**	

16. Quit Attempts During the Study Protocol:

At each session, we will ask the participant if he/she is currently abstaining from smoking and/or vaping with the intention of quitting. If the answer is no, then we will also ask if he/she is planning to quit smoking and/or vaping prior to his/her next scheduled visit.

16.1. If a participant is currently abstaining from smoking and/or vaping with the intention to quit we:

- Encourage participant to continue abstaining.
- Schedule the participant for normal weekly visits, but do not conduct puff topography, preference task or product evaluation tasks
- Provide the participant with the '*Clearing the Air*' manual and smoking cessation resources

- Give the participant the option to take home he/she's preferred amount of study product, up to the full amount (baseline CPD), that they would like to take, rather than require him/her to take the full amount.
    - If the participant choses to take home the study product we have him/her sign a form acknowledging that tobacco product availability could be detrimental to the quit attempt. We also recommend that he/she puts the product "away" at home as to avoid unwanted cues to smoke.
- If the participant chooses not to take home the study product, we have him/her contact the lab if he/she lapses and would like to pick up the study product prior to his/her next visit.

16.2. If a participant is planning to quit smoking or vaping, but has not initiated the quit attempt we

- Ask if he/she has identified a target quit date and, if so, what that target date is
- Provide the participant with the '*Clearing the Air*' manual and smoking cessation resources
- Provide the participant with he/she's preferred amount of study product, up to the full amount (baseline CPD), that they would like to take. We also recommend that on the target date he/she puts the product "away" at home as to avoid unwanted cues to smoke.
- If the participant choses to take home any amount of the study product, we have him/her sign a form acknowledging that tobacco product availability could be detrimental to the quit attempt.

17. Potential risks of participation

1. Survey Questionnaires: The interview will include questions about medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could make the participant feel uncomfortable.
2. Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results.
3. Smoking Cigarettes: All cigarettes are detrimental to a person's health and can lead to severe or fatal medical problems including:
    a. Cardiovascular Diseases: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    b. Respiratory Diseases: Emphysema, bronchitis, tuberculosis and chronic airway obstruction
    c. Cancers: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia
    d. Diabetes
    e. Abnormal immune function, rheumatoid arthritis
    f. Other Health Risks Associated with Smoking: Including but not limited to infertility, tubal pregnancy, Sudden Infant Death Syndrome (SIDS), birth defects, lower bone density in postmenopausal women, hip fracture in women, male sexual dysfunction; age-related macular degeneration, vision problems.

g. Changes in blood pressure and/or heart rate
h. Death

4. Smoking study cigarettes: In addition to the above medical problems, participants may experience some minor adverse health effects such as headaches or experience withdrawal symptoms which are listed below. Due to the altered nicotine levels, there could be a change in their cigarette use including the way they inhale the smoke or an increase in the number of cigarettes smoked per day. This increased rate of smoking may persist after completing the study. Smoking the study cigarettes does not provide any less risk than their usual brand cigarette and could pose increased health risks. Participants may also experience increases in levels of carbon monoxide, a gas from smoke. The study cigarettes are made from genetically modified tobacco plants. A recent toxicological analysis of these cigarettes showed that the concentrations of many harmful tobacco constituents, including tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, ammonia, and toxic metals, was similar to the concentrations of these constituents in commercial cigarettes (Richter et al., 2016).
5. Vaping Devices: Vaping devices can expose users to several chemicals, including nicotine, carbonyl compounds, and volatile organic compounds, known to have adverse health effects. The health effects and potentially harmful doses of heated and aerosolized constituents of vaping devices, including solvents, flavorants, and toxicants, are not completely understood. Vaping device aerosol is not harmless although it generally contains fewer toxicants than combustible tobacco products. Specific potential known risks include:
    a. E-liquids may contain nicotine contain nicotine which may contribute to some of the disease associated with smoking.
    b. The most common side effects related to vaping device use are changes in taste, mucus in throat/sinus, dry mouth, dry cough, throat irritation, sore throat, mouth ulcers, dizziness, headache, seizures, and nausea. Subjects are told to stop use of e-cigarette (or other nicotine products) and promptly notify study staff if they have loss of consciousness, memory lapse, change in mental status, confusion, tremor, shaking, or seizure.
    c. While uncommon, batteries from vaping devices have exploded/ignited and injured users.
    d. Vaping devices can overheat and present a burn risk if the device is turned on repeatedly. Subjects are told to be careful if storing the device in a place where the button might be accidentally pressed often.
    e. Defective cartridges, tanks or devices may leak e-liquid. If this should happen, wash the exposed area to remove the e-liquid immediately.
    f. Ingestion of e-liquids containing nicotine can cause acute toxicity and possible death if the contents of refill cartridges containing nicotine are consumed. Subjects are told to keep vaping devices and all e-liquid cartomizers away from pets and children. Instructions are provided to call the Poison Control Center (1-800-222-1222) immediately and contact study staff if e-liquids are ingested. For skin exposure we recommend washing well with soap and water for 10-15 minutes.
    g. Allergic reactions to propylene glycol and vegetable glycerin have been reported. Chemicals used to flavor foods are also a risk for allergic reactions. We will ask

subjects if they have had previous adverse reactions to vaping and/or allergic reactions to food and provide that information to the medical monitor to review as part of determining eligibility.

h. Recent reports of seizure and severe lung problems associated with vaping are being evaluated by the CDC and the FDA. While current evidence is not conclusive of causality, it is prudent to inform potential subjects of this on-going investigation and be alerted to the symptoms of lung disease. These symptoms include: cough, shortness of breath, chest pain, nausea, vomiting, abdominal pain, and fever. One should promptly seek medical attention for any health concerns. Subjects will also be advised to use only the study product we have provided to them and to not alter the device or add any substances to e-liquids. We will keep participants informed as the additional information is provided by the CDC and FDA.

6. Continued use of vaping devices: As part of this study, participants will try a vaping device on multiple occasions and can use a vaping device as much as they like, outside of the lab, over a 12-week period. This product may contain nicotine, an addictive chemical. It is possible that this experience could lead to long-term use of vaping devices after the trial is over.
7. Nicotine Withdrawal: Participants may experience smoking withdrawal symptoms during this study. The symptoms can be uncomfortable but are typically of minimal risk. Smoking withdrawal symptoms include:
    a. Anger, irritability, frustration
    b. Anxiousness, nervousness
    c. Depressed mood or sadness
    d. Desire or craving to smoke
    e. Difficulty concentrating
    f. Increased appetite, hunger or weight gain
    g. Insomnia, problems sleeping or awakening at night
    h. Restlessness
    i. Impatience
    j. Constipation
    k. Dizziness
    l. Coughing
    m. Dreaming or nightmares
    n. Nausea
    o. Sore Throat
8. Returning to Regular Smoking: It is possible that if participants return to smoking their usual brand of cigarette at the end of the study they may experience mild and transient nausea, dizziness, and lightheadedness.
9. Risk to Fetus**:** Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), early childhood behavioral problems, altered lung development, and a possible propensity for addiction. Although unknown, adverse effects could occur with the use of vaping devices.

10. Changes in blood pressure and/or heart rate: Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate.
11. Changes in mood, emotions and psychiatric symptoms: Smoking and nicotine can affect a person's mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine use or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
12. Smoking and oral contraceptives in women: Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician. Smoking while using oral contraceptives can increase the risk of having a cardiovascular event such as a heart attack or stroke. Additionally, there is a potential risk of thrombosis associated with hormonal therapy (including contraceptives) and smoking.
13. Smoking and medications: Quitting smoking can greatly benefit participants' health. However, changes in smoking can lead to changes in how well some medications work. Participants should disclose all medications they are taking. We also recommend that participants discuss any planned or actual changes in how much they smoke with their doctor, especially if they are taking any medications for psychiatric, cardiovascular, or other serious diseases.
14. Unforeseen risks: There may be additional unforeseen short and long-term risks of participation.

18. Avoiding Risks to Fetus

If participants choose to be sexually active, they are advised to use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Female participants with child-bearing potential will be tested for pregnancy at Screening, Randomization, and Visits 04, 08 and 12. If a participant becomes pregnant during the study, she will be withdrawn from the study. Approximately 30 days after being withdrawn or having a positive pregnancy test at Visit 12, the research staff will call the participant to confirm her due date. The licensed medical monitor will follow-up with the participant after delivery to ask questions about the baby's health.

19. Expected benefits of participation

There are no immediate benefits from participating in the study. The information obtained from this study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health.

20. Suicidality/Mental Health Monitoring

Participants who make any response other than "not at all" on the suicidal ideation question of the Prime MD (Question 1i), indicate suicidal ideation, have attempted suicide in the past month, or have had a suicide attempted in the past 5 years on the MINI suicide subscale will not be eligible to participate in the study. If the participant has attempted suicide between 6-10 years ago, then the LMM must approve eligibility. To determine if a participant is in immediate danger, staff will ask the participant two questions to determine level of risk: "Are you feeling suicidal?" and "Do you have a plan to kill yourself today?" If the participant has a plan to kill himself/herself, staff will put the participant in contact with the suicide prevention hotline (Durham Center Crisis Line at 1-800-510-9132; Philadelphia Suicide Prevention Hotline: 215-686-4420 or UPenn's HELP line: 215-898-HELP 4357). If the participant refuses to talk to the hotline and leaves, the study staff will call 911. They will also contact the Study Coordinator and Site PI to inform them of the situation as soon as possible. If the participant does not have a plan to kill himself/herself, the study staff will recommend he/she speaks with the suicide hotline. The visit will continue as normal, but the participant will not be eligible for the study. The participant will be paid $30 and provided with local mental health resources. The on-site clinician will be available by phone for consultation within 24-hours.

Additionally, any participant whose score on the Prime MD indicates Major Depressive Disorder will be administered the Beck Depression Inventory (BDI) and the GAD 2 week monitoring on paper. The BDI will be submitted, along with the Prime MD, Brief Medical History Questionnaire, Brief Medical History Follow-up Questionnaire, and the MINI suicide subscale to the licensed medical monitor for eligibility review. If he/she determines a participant with Major Depressive Disorder is eligible for study participation, the participant will complete the BDI each visit to monitor changes in his/her mood.

21. Adverse Events (AE)

21.1. Identifying Adverse Events

While participating in the trial, adverse events and concomitant medications will be assessed at every study visit and vital signs and carbon monoxide will be measured. Adverse events will typically be identified during the administration of the Health Changes Questionnaire and Respiratory Health Questionnaire, and in some cases during the administration of the CESD. Other events may be identified from physiological study measures or by spontaneous reports during non-scheduled assessments. The medical monitor is notified about all AEs within 10 days.

Questionnaire items that will be reviewed:

1. Health Changes Questionnaire
    1. ***Have you had any negative changes in your physical or mental health since your last visit? If yes, briefly describe.***
    2. ***Since your last visit, have you received any form of medical care? If yes, briefly describe.***

    No new AE report will be required if one or more conditions below are met and the description does not otherwise meet the definition of an AE.

a. Existing AE already open for reported symptom
b. Pre-existing condition without increase in severity or frequency of symptoms (brief medical history will be updated if not previously reported).
c. Nicotine withdrawal symptoms that don't meet AE criteria

A. The following withdrawal symptoms are considered expected withdrawal symptoms and are not considered AEs

1. Desire or craving to smoke
2. Restlessness
3. Impatience
4. Increased appetite, hunger, weight gain*

*If a participant indicates any clinical behaviors such as binging or purging this should be recorded as an Adverse Event and the PrimeMD should be completed.

B. The following withdrawal symptoms would be considered an AE if the participant indicated the symptom had a significant impact on your daily life, caused a major disruption of functioning, or took any medication for it.

1. Anger, irritability, frustration
2. Difficulty Concentrating
3. Insomnia
4. Nightmare/Night Terrors
5. Depressed (sad) mood*
6. Anxious (nervous) mood*

*If a depressed (sad) mood and an anxious (nervous) mood AE is reported, the participant will complete the Prime MD and be assessed for suicidality.

d. Received preventative or follow-up medical care.
e. Other (explain).

2. Respiratory Health Questionnaire: ***In the past week, have you experienced any health problems, such as cold, flu, or other respiratory illness that would affect these respiratory symptoms?***

No new AE report will be required if one or more conditions below are met and the description does not otherwise meet the definition of an AE.

a. Existing AE already open for reported symptom
b. Pre-existing condition without increase in severity or frequency of symptoms (brief medical history will be updated if not previously reported; e.g., seasonal allergies).

3. CESD: If the participant **scores 16 or higher and is not already being monitored for depression**, a 'Adverse Event Form' should be completed and the LMM will provide information regarding follow-up. If there is already an open event, information will be added to the existing 'Adverse Event Form.'

Physiological data that will be reviewed:

1. CO level: The 'Adverse Event Form' should be completed if the average CO within a visit is:
    - CO is greater than 50 ppm if CO at Baseline is < 20 ppm.
    - CO is greater than 60 ppm if CO at Baseline is 20 – 34 ppm.
    - CO is greater than 70 ppm if CO at Baseline is 35 – 49 ppm.
    - CO is greater than 80 ppm if CO at Baseline is 50 – 64 ppm.
    - CO is greater than 90 ppm if CO at Baseline is 65 – 80 ppm.
2. Blood Pressure:
    - The 'Adverse Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual blood pressure measurement during the same visit is **at or above 160 SBP or 100 DBP.**
    - The 'Adverse Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual blood pressure measurement during the same visit **is below 90 SBP or 50 DBP.**
3. Heart Rate:
    - The 'Adverse Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual heart rate measurement during the same visit is **at or above 105 bpm.**
    - The 'Adverse Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' should be completed if an automatic **and** subsequent manual heart rate measurement during the same visit is **below 45 bpm.**

22. Management of SAEs and Other Study Risks

The site medical monitor(s) will review all AEs. A study participant may be discontinued from the study if the medical monitor and/or PI determine it is the best decision in order to protect the safety of a participant. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an AE/SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes. Any AE that remains open will be reviewed and closed at the 30 day follow-up visit.

23. Reporting of SAEs to the IRB, FDA, and NIDA

Serious adverse events (SAEs) as defined in 21 CFR 312.32 (death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly/birth defect, required intervention to prevent permanent impairment or damage (devices), other serious (important medical outcomes)) that are related or possibly related to study participation will be reported to the Administrative Core, all site IRBs, the NIDA Scientific Officer (Kevin Walton, PhD), the NIDA Project Officer (Ann Anderson, MD), FDA, and the Data Safety and

Monitoring Board. All Site IRBs require that fatalities related to the study be reported within 24 hours, that all other SAEs be reported within 5 business days. Reports of all SAEs will also be documented within NIDA's SAE data monitoring system, or SAETRS, within 72 hours.

24. Reporting of IRB Actions to NIDA

Actions taken by the local IRBs in response to SAEs will be reported to NIDA in the annual noncompetitive continuation application, as will reports of changes or amendments to the protocol as a result of an SAE. Recommendation for trial discontinuation, for significant changes or amendments to the protocol, or other significant findings as a result of an SAE will be reported immediately to the NIDA Scientific Officer (Kevin Walton, PhD) and Project Officer (Ann Anderson, MD) by the Project PI.

25. Reporting Changes or Amendments to the Protocol

Any changes or amendments to the protocol made in response to adverse events/SAEs will be discussed with Eric Donny, PhD and Dorothy Hatsukami, PhD, and then requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. The DSMB and FDA will be notified about any significant changes to the protocol. NIDA will be informed of any approved changes in protocol by documentation in the noncompetitive continuation application. Changes that significantly alter the scope of the research or the ability of the research to achieve its specific aims will be submitted to Eric Donny, PhD and Dorothy Hatsukami, PhD, the DSMB, FDA, and NIDA for approval prior to implementation.

26. Withdrawal or Monitoring of Participants

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1. Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2. DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
3. Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4. Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5. Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at the Randomization Visit, she will be withdrawn from the study, and this event will remain open until delivery. At that time the licensed medical monitor will contact the participant to ask a

few questions about the baby's health and will update the open 'Adverse Event Form'. A positive pregnancy test at follow-up will trigger an 'Adverse Event Form' to be completed but will not result in withdrawal since she is no longer receiving study product.

6. Expired breath carbon monoxide increase: A participant will be withdrawn from the study if their CO reading is 100 ppm or greater.

The following will be monitored and can lead to the participant being withdrawn by the PI or Licensed Medical Monitor:

1. Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-enrollment: 1) BP is at or above 160 SBP or 100 DBP, 2) BP is below 90 SBP or 50 DBP 3) HR is at or above 105 bpm, 4) or below 45 bpm.
2. Changes in tobacco product use: if during the weekly visits, participants self-report a greater than 100% increase in cigarette per day (total cigarettes, including study and non-study cigarettes) relative to baseline, or a 50% increase in cigarettes per day relative to baseline that is accompanied by an average daily use of 2 ml e-liquid or more."
3. Expired breath Carbon Monoxide increase: An 'Adverse Event Form' will be documented and the participant will be monitored by the medical monitor if CO exceeding the following criteria based on Baseline CO:
    a. CO is greater than 50 ppm if CO at Baseline is < 20 ppm.
    b. CO is greater than 60 ppm if CO at Baseline is 20 – 34 ppm.
    c. CO is greater than 70 ppm if CO at Baseline is 35 – 49 ppm.
    d. CO is greater than 80 ppm if CO at Baseline is 50 – 64 ppm.
    e. CO is greater than 90 ppm if CO at Baseline is 65 – 80 ppm.
4. Medication changes: If a participant begins taking any of the exclusionary medications or other medications that could potentially have a smoking-drug interaction post- enrollment, the licensed medical monitor will determine how best to monitor and minimize potential risks (including withdrawal if warranted). We will also recommend that a letter be sent to the participant's physician (with their consent), making them aware of the potential changes in smoking that could occur as a result of participation in the study.
5. Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical monitor to determine whether continued participation in the study is appropriate.
6. If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other smoking research studies that could affect the primary outcome measures, does not follow study instructions, etc., then the PI can withdraw him/her from the study at the PI's discretion.
7. If a participant fails to attend his/her Randomization Visit within the 21-day allowable visit window, he/she will not be eligible to reschedule this visit or continue participation in the study.
8. If there is reason to believe the participant is sharing the study product with other people.

If a participant chooses to withdraw from the study at any time, we will them to return to the lab to return study product and equipment and to receive their final study payment. We will also ask participants who have been randomized if they would like to complete the end of study questionnaires.

27. Investigational Tobacco Product

The Co-Directors of this Center grant, Drs. Donny and Hatsukami, have submitted an Investigational Tobacco Product (ITP) application to the FDA to cover the experimental cigarettes being used in this study.

28. Study Endpoints / Outcomes

28.1. Primary Endpoints:

- Total number of cigarettes smoked per day (i.e. study plus non-study cigarettes) as measured by daily Interactive Voice Response (IVR) phone calls. The total number of cigarettes smoked per day will be averaged using the last 7 days prior to the Week 12 visit. We note that subjects have the opportunity to correct data entry errors in IVR from calls made since the last visit at each visit (for example, if a subject entered 100 cigarettes instead of 10 cigarettes). In these cases, the original IVR data will be replaced with the corrected data to create a final, cleaned version that will be used for analysis (herein called "IVR-Revised"). A secondary, repeated measures analysis will also be completed using the mean of the total number of cigarettes smoked per day at each visit, calculated using IVR calls from the previous 7 days. In the event that two visits were less than 7 days apart, then the average will be calculated using only days since the last visit.

28.2. Secondary Outcomes:

- Cigarette smoke exposure: mercapturic acid CEMA
- Smoke-free days: the number of days not smoking any combustible products based on IVR-Revised

28.3. Exploratory Outcomes:

- Cigarette characteristics: CES subscale score for Satisfaction
- Discomfort/dysfunction: MNWS total
- Vaping device use: number of days using assigned vaping device (IVR)
- Study cigarettes per day (CPD): the mean cigarettes smoked per day based on 7 days' Daily Interactive Voice Response (IVR)-Revised data before the week 12 visit.
- Cigarette dependence: Total scores on the FTND

- Compliance/retention: Non-study cigarette use (IVR), urinary anatabine, drop-out rate
- Nicotine exposure: urinary total nicotine equivalents
- Cigarette smoke exposure: breathe CO, urinary mercapturic acids, puff topography
- Relative reinforcement: Preference Task, Purchase Task
- Cigarette dependence: WISDM Primary Subscales, Penn State Smoking Questionnaire, and PATH Smoking Dependence questions
- E-cigarette dependence: Penn State E-cigarette questionnaire, PATH Vaping Dependence questions
- Hypothetical cigarette and vaping device use: Purchase Task, Predicted Behavior Questionnaire
- Discomfort/dysfunction: urge to use questionnaire, CES-D total score
- Vaping device use: intensity (puff/day) of use of the assigned vaping device (IVR), e-liquid mls used per week; e-liquid flavor preferences
- Smoking/vaping context: Environmental and Social Influences on Tobacco Use, Context of Product Use
- Product expectancies: Vaping Utility Questionnaire, Smoking and Vaping Expectancies Questionnaires
- Perceived risk: Perceived Health Risk Questionnaire
- Other health-related behaviors: Breath alcohol, urine drug screen, Alcohol Use Questionnaire, Drug Use Questionnaire, weight
- Cigarette characteristics: CES subscale scores
- Intention to quit: Stages of Change, Contemplation Ladder, Quit Attempts
- Post-intervention changes in tobacco use behavior: 30-day tobacco use questionnaire
- Qualitative Interview: Themes related to product use patterns, e-liquid flavor selection, non-compliance and general study feedback

28.4. Safety Outcomes:

- Potential adverse consequences: Change in mental (CES-D) or physical health (Respiratory and Global Health Questionnaire, Health Changes Questionnaire, weight)
- Measures of cardiovascular function: Heart rate, blood pressure
- Increased nicotine exposure as indicated by 100% increase in total nicotine equivalents relative to baseline or a 50% increase in cigarettes per day relative to baseline that is accompanied by an average daily use of 2ml e-liquid or more.
- Adverse events

29. Statistical Approach

This is a 2x2x2 factorial design in which participants will be randomized with equal probability to one of eight groups. Randomization will be stratified by age (18-24 vs. 25+) and menthol preference; a set number/percentage of either age and menthol vs. non-menthol preferring smokers will not be enforced. All analyses described below will follow the intent-to-treat principle (i.e. subjects will be analyzed according to their randomized treatment assignment regardless of their compliance) unless otherwise noted.

Our primary objective is to test the main effects of cigarette nicotine content, e-liquid nicotine content and e-liquid flavors, as well as the interactions among these factors. The *primary endpoint* will be total CPD (i.e. study plus non-study CPD) based on IVR-Revised. The primary analysis will compare CPD by factor at the week 12 visit using linear regression. Treatment groups should be balanced at baseline, and as a result our primary analysis will only adjust for baseline CPD, week and the three stratification factors (site, age, and menthol preference). This will be considered the "unadjusted model" for the purposes of this document. We will start with a model that includes all two-way interactions between the three factors (note: the three way interaction will not be considered). Two-way interactions that are not significant will be removed from the model and the final model will include the three factors, any two-way interactions significant at the 0.05 levels, baseline CPD, and the three stratification factors. The estimation and testing of main effects in the presence of significant interactions will be completed within levels of the other factor, otherwise, global estimates of the main effects will be obtained. Whenever possible, secondary endpoints will be analyzed following the approach to testing the main effects and interactions described above. Biomarkers of toxicant exposure are expected to be skewed and will be analyzed on the log scale. Likewise, exploratory endpoints will be analyzed following the approach outlined above using a linear mixed model or logistic regression, as appropriate, depending on the type of endpoint (continuous, binary). Finally, we will complete subgroup analyses following the approach described above within each subgroup (age: 18 – 24 vs. 25+; menthol preference; sex). We will not use formal multiple comparison adjustments for secondary endpoints because we have included only 2 outcomes that are likely correlated with each other and the primary endpoint. Likewise, we will not correct for multiple comparisons for our subgroup analyses as they are considered exploratory.

Study staff will make every effort to minimize missing data in the proposed clinical trial. The success of our previous and ongoing trials suggests that missing data will be minimal. Nevertheless, we plan to complete a sensitivity analysis to evaluate the impact of missing data on trial conclusions.

We will compare subjects with and without missing data in order to identify baseline covariates associated with missing data. Our primary approach to handling missing data will be multiple imputation where missing values are imputed using regression models developed from baseline covariates (Little and Rubin, 2002). Daily IVR data will be averaged within a week using complete observations (i.e. we will average the number of cigarettes smoked per day for complete calls). In our previous work (Donny et al., 2015), 90% of weeks had 0 or 1 missed call, while 4% of weeks were completely missing, which suggests that an alternate approach to handling sporadically missed calls will only impact a small number of weeks for the entire trial. Missing

weekly average IVR data (i.e. when all calls in a week are missing) will be analyzed using multiple imputation.

In addition, we will conduct a sensitivity analysis of the primary and secondary endpoints using baseline-carried-forward and last-observation carried forward. The results of these analyses will be compared to the primary analysis to evaluate the robustness of our conclusions.

For the qualitative data, we will use grounded theory to develop hypotheses related to the topics of interest. Interviews will be audio-recorded and transcribed verbatim. The interviews will be analyzed using open and axial coding. Themes will emerge during data analysis, which will be ongoing throughout the project.

30. Power Analysis

We will enroll 480 subjects (n=60/group) and assume 75% retention at week 12 (i.e. 360 completers) based on our current and previous trials. Power calculations are presented for testing the main effects and the interactions between cigarette nicotine content and e-cigarette nicotine concentration or flavor. Effect size estimates were based on our previous studies of VLNC cigarettes and the assumption that the main effect of e-liquid nicotine content and the interaction between e-liquid nicotine content and cigarette nicotine content will be similar to the effect of cigarette nicotine content. This assumption is supported by the results of Donny and Jones, who found that the effect of transdermal nicotine on use of VLNC cigarettes was as large as the main effect for cigarette nicotine content (Donny & Jones, 2009). The impact of flavors is largely unknown, therefore, we assumed an effect size similar to e-liquid nicotine content ([A] in table below) as well as one half as large ([B] in table below). All power calculations were completed assuming a type-I error rate of 0.05. Power calculations for the main effect were completed in PASS 13. Power for testing interactions was calculated by simulation and is consistent with the well-known theoretical relationship between the power for testing main effects and the power for testing interactions.

Outcome	Effect size shown as Diff (SD)	Power - Full Sample				Power - Subgroups[C]	
		Main Effect[A]	Main Effect[B]	Interaction[A]	Interaction[B]	Main Effect[A]	Interaction[A]
Primary Outcome							
CPD[1]	6.3 (7.2)	0.99	0.99	0.99	0.54	0.99	0.83
Secondary Outcomes							
FTND[1]	1.31 (1.77)	0.97	0.94	0.94	0.41	0.94	0.69

Log(CEMA) [1]	0.51 (0.92)	0.96	0.73	0.73	0.25	0.74	0.44

[A] Effect size for flavor equal to effect size for nicotine. [B] Effect size for flavor equal to half the effect size for nicotine.
[C] Power calculations for our pre-planned subgroup analyses are based on the assumption of 50% of participants in each subgroup defined by age, sex, and menthol status. We are not forcing balance for any of these factors and we therefore acknowledge that the actual power will be larger for subgroups with more than 50% of the sample and lower for subgroups with less than 50% of the sample. [1] The hypothesized differences for CPD, FTND and log(CEMA) are based on the differences observed between the immediate reduction and control groups at 12 weeks in Hatsukami et al. (submitted)

31. Subject Identifier

The subject identifier is an alpha-numeric combination. Example: M-G001 would be Wake Forest University's first subject.

31.1.1. Project Identifier

G= Project 2

31.1.1. Site Identifier

M = Wake Forest School of Medicine
E = University of Pennsylvania

31.1.2. Subject ID

001-899

31.1.3. Data Collection Time Points Identification Numbers

92= Screening Visit
91=Baseline Visit 1
00=Randomization
01= Week 1 visit
02= Week 2 visit
03= Week 3 visit
04= Week 4 visit
06= Week 6 visit
08= Week 8 visit
10= Week 10 visit
12= Week 12 End of Intervention visit

30= 30-day follow-up visit
Additional visit (AV1, AV2, etc)
86 = Termination Visit

32. Summary of Measures

Procedures Table	Platform/Source	SCRN 92	BL 91	RAN 00	Week 01	Week 02	Week 03	Week 04	Week 06	Week 08	Week 10	Week 12	Follow-Up 30
Anatabine (spot urine)	UMN Biomarker Core		X	X	X	X	X	X	X	X	X	X	X
Mercapturic Acids (1st void urine)	UMN Biomarker Core		X	X				X		X		X	X
Total Nicotine Equivalents (1st void urine)	UMN Biomarker Core		X	X				X		X		X	X
Nicotine Metabolite Ratio (saliva)	UMN Biomarker Core		X										
Carbon Monoxide	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
Urinary Cotinine Test	Paper and REDCap	X											
BrAC	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
Toxicology Screen	Paper and REDCap	X										X	
OTHER ASSESSMENTS													
Identifying Information Form	Paper and Access	X											
Brief Medical History Questionnaire	Paper and REDCap	X											
Brief Medical History Follow-Up Questionnaire (if needed)	Paper and REDCap	X											
Prime MD	Paper and REDCap	X											
MINI Suicide Subscale	Paper (Source Only)	X											
Tobacco Use History and Exposure	Paper and REDCap	X											
Demographics Questionnaire	REDCap	X											
Smoking Cessation Therapy Use	Paper and REDCap	X											

Procedure Table	Platform/Source	SCRN 92	BL 91	RAN 00	Week 01	Week 02	Week 03	Week 04	Week 06	Week 08	Week 10	Week 12	Follow-Up 30
Smoking Stages of Change	Paper and REDCap	X						X		X		X	X
ALCOHOL AND DRUG USE													
Drug Use (12 months)	Paper and REDCap	X											
Drug Use History (1 month)	Paper and REDCap	X						X		X		X	X
Alcohol Use (12 months)	REDCap	X											
Alcohol Use (1 month)	REDCap	X						X		X		X	X
DEPRESSION MONITORING													
Beck Depression Inventory (if needed)	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
CES-D	REDCap	X						X		X		X	
GAD 2 week monitoring (if needed)	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
HEALTH MONITORING													
Concomitant Medications	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
Health Changes Questionnaire	Paper and REDCap		X	X	X	X	X	X	X	X	X	X	X
Respiratory Health Questionnaire	REDCap		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Form (if needed)	Paper and REDCap		X	X	X	X	X	X	X	X	X	X	X
SMOKING BEHAVIOR													
Tobacco Daily Diary (IVR; in field, enrolled at screening)		Enroll	X	X	X	X	X	X	X	X	X	Un-enroll	
Puff Topography: Usual Brand	CReSS	X											
Puff Topography: Study Cig	CReSS				X						X		
Puff Topography: Study Vape	Custom				X						X		
IVR Review and TLFB Questionnaire, if needed	Paper and REDCap		X	X	X	X	X	X	X	X	X	X	

Procedure Table	Platform/Source	SCRN 92	BL 91	RAN 00	Week 01	Week 02	Week 03	Week 04	Week 06	Week 08	Week 10	Week 12	Follow-Up 30
Context of Product Use: Baseline	REDCap			X									
Context of Product Use: Experimental	REDCap							X		X		X	
Predicted Behavior Questionnaire	REDCap											X	
Intention to Quit Smoking + Vaping	Paper and REDCap		X	X	X	X	X	X	X	X	X	X	
30 Day Tobacco Use Questionnaire	Paper and REDCap												X
Craving/Withdrawal													
MNWS	REDCap			X	X	X	X	X	X	X	X	X	
Urge to Use: Baseline	REDCap			X									
Urge to Use: Experimental	REDCap				X	X	X	X	X	X	X	X	
Smoking and Vaping Reinforcement/Dependence													
Preference Task	REDCap			X									
Cigarette Dependence	REDCap			X				X		X		X	X
Vaping Dependence	REDCap			X				X		X		X	X
Purchase Task Usual Brand	REDCap		X										
Purchase Task Study Cigarette + Vape	REDCap											X	
PRODUCT EVALUATION													
Cigarette Evaluation Scale: Usual Brand	REDCap		X										
Cigarette Evaluation Scale: Study Cig.	REDCap			X		X		X		X		X	
Vaping Evaluation Scale: Study Vape	REDCap			X		X		X		X		X	
Perceived Health Risk: Usual Brand	REDCap		X										

Procedure Table	Platform/Source	SCRN 92	BL 91	RAN 00	Week 01	Week 02	Week 03	Week 04	Week 06	Week 08	Week 10	Week 12	Follow-Up 30
Perceived Health Risk: Study Products	REDCap			X		X		X		X		X	
Environmental and Social Influences on Tobacco Use Questionnaire	REDCap		X									X	
Smoking Expectancies Questionnaire	REDCap		X									X	
Vaping Expectancies Questionnaire	REDCap		X									X	
Vaping Utility	REDCap		X									X	
End of Study Questionnaire	REDCap											X	
Qualitative Interview Guide	Paper/Audio												X
PHYSIOLOIGCAL ASSESSMENTS													
Height	Paper and REDCap	X											
Weight	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (Female Participants)	Paper and REDCap	X		X				X		X		X	
HR/BP	Paper and REDCap	X	X	X	X	X	X	X	X	X	X	X	X

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