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Title: Impact of e-cigarette characteristics on reinforcement and tobacco use patterns among current smokers
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Abstract

The prevalence of e-cigarette use has increased dramatically in recent years. Because e-cigarettes deliver fewer toxicants than combustible cigarettes, they likely offer improved health outcomes for current smokers who switch completely. However, many smokers who try using e-cigarettes do not switch completely, abandoning e-cigarettes altogether or continuing to use both products. Thus, it is important to understand the factors that lead to these variable tobacco use patterns. One of the primary determinants of e-cigarette uptake and changes in smoking behavior is the reinforcement value delivered by e-cigarette products. Product characteristics that impact nicotine delivery and sensorimotor characteristics are most likely to impact relative reinforcement value. Two of the primary product-level determinants of nicotine delivery and sensorimotor characteristics are the nicotine concentration of e-liquid and the power of the e-cigarette device. The proposed research project will investigate the impact of these characteristics on relative reinforcement value and tobacco use patterns. Current smokers (n=180) will receive an e-cigarette and e-liquid to take home and use over a three-week period. In a double-blind 2x2 design, participants will be randomly assigned to receive a low (3 mg) or high (12 mg) nicotine concentration, and either a low (20 W) or high (40 W) e-cigarette power setting. Participants will return to the lab each week to complete laboratory assessments of relative reinforcement value and provide breath and urine samples for biomarker assessments of smoke and nicotine exposure. Participants will also complete daily electronic diaries assessing tobacco use. Thus, the proposed design includes both lab-based and ecological assessments of reinforcement and tobacco use. The results from this project will provide critical information about the relationship between different e-cigarette products and tobacco use patterns, as well as inform the Food and Drug Administration about how to regulate tobacco products with the goal of improving public health. The K12 candidate, Dr. Tracy Smith, aims to develop an independent research portfolio that seeks to understand how 1) contextual, individual, and product characteristics contribute to the use of tobacco products, and 2) we can leverage this information to improve public health through tobacco regulation, policy, and public health interventions. The proposed research project described here, along with clear training objectives, will provide the skills necessary to achieve that goal. Training objectives include gaining expertise in non-cigarette tobacco products, tobacco control research, applied research methodologies, and grant-writing. A strong team of mentors have been assembled with expertise in each of these areas. MUSC provides a stellar training environment to allow K-awardees to transition to independent research funding. The training described here is a clear progression from Dr. Smith's prior work, provides necessary skills for obtaining research independence, and will launch Dr. Smith's research independence in substantial, measurable ways.

Keywords: Tobacco addiction, Electronic cigarettes, Reinforcement value

Specific Aims

E-cigarette use in the United States has risen dramatically [2]. Because e-cigarettes deliver a heated aerosol rather than combusted tobacco, they offer the potential for lower toxicant exposure than combustible cigarettes [3-6], and likely carry reduced health burden for smokers who switch completely from cigarettes to e-cigarettes [3, 6, 7]. Thus, any public health benefit of e-cigarettes, if there is one, will depend on if and how smokers use e-cigarettes. However, many smokers who try e-cigarettes discontinue use after a short trial period, or continue use of both e-cigarettes and cigarettes (i.e., dual use) [8-10]. It is therefore important to understand the factors that impact uptake of e-cigarettes and changes in smoking behavior following uptake. The e-cigarette marketplace is ever-expanding and there is high variability in both devices and e-liquids [11]. Yet the impact of product characteristics on uptake is poorly understood. **Indeed, a recent report from the National Academy of Sciences, Engineering, and Medicine listed the impact of e-cigarette product characteristics on behavior as a top research priority** [12]. The present application focuses on specific product characteristics that impact the most important determinant of use: relative reinforcement value.

Reinforcement value is the perceived magnitude of a reward. For e-cigarettes, this value is likely a function of both nicotine delivery and sensorimotor cues. Nicotine is the primary pharmacological reinforcer for tobacco use [13]. Nicotine delivery for e-cigarettes is impacted by at least two product characteristics. First, e-cigarettes contain liquid that can be purchased with a wide range of nicotine concentrations. Second, devices vary in how much power is delivered to the heating element. These two characteristics, nicotine concentration and device power, work together to impact the nicotine delivery of the aerosol that is delivered to the user. Survey evidence suggests a negative correlation between the power of a device and the chosen nicotine concentration [14, 15], likely because users modify their choice of concentration and power such that optimal levels of nicotine are delivered. Aside from nicotine delivery, both the nicotine concentration and the power of the device are important determinants of the sensorimotor cues associated with e-cigarette use, such as the “throat hit” a smoker feels when taking a puff, and the temperature and volume of the delivered aerosol. Despite the importance of these characteristics, no study has experimentally investigated the interaction between these two characteristics on reinforcement value and tobacco use. ***The purpose of this application is to use both lab-based and naturalistic methods to understand how nicotine concentration and device power interact to impact relative reinforcement value and tobacco use patterns.***

Within a 2x2 between-subjects design that manipulates nicotine concentration (3 vs. 12 mg/ml) and device power (20W vs. 40W), daily smokers with limited e-cigarette experience (n=180) will receive e-cigarettes to use ad libitum over a three-week period. Methods include both naturalistic/ecological assessments (daily diaries, an e-cigarette device that captures topography) and experimental sessions to examine reinforcement (preference and purchase tasks). Biomarkers will corroborate self-reported indices of use. Because the public health impact of e-cigarette use is ultimately dependent on changes in cigarette smoking behavior, our primary focus is on changes in smoking and the reinforcement value of cigarettes. We do however test for differences in uptake and reinforcement value of e-cigarettes.

Specific Aim 1: To understand the impact of nicotine concentration and device power on cigarette smoking (cigarettes smoked per day; CPD) and smoke exposure (expired breath carbon monoxide; CO). Hyp1: There will be an interaction such that a higher (vs. lower) nicotine concentration will produce greater reductions in CPD and CO when device power is low, and a lower nicotine concentration will produce greater reductions in CPD and CO when device power is high. Hyp2: Parallel analyses will test the main and interactive effects of nicotine concentration and device power on e-cigarette use (hypothesizing more puffs per day).

Specific Aim 2: To understand the impact of nicotine concentration and device power on relative reinforcement value (choices to smoke versus use an e-cigarette in a lab-based preference task, demand for each product on a hypothetical purchase task). Hyp3: There will be a similar interaction such that a higher nicotine concentration will result in fewer choices to smoke a low power device, and a lower nicotine concentration will result in fewer choices to smoke in a high-power device.

A. Significance

A1. The Rise of E-cigarettes and their Impact on Public Health:

E-cigarettes are now used by 5.5% of adults, and 8.9% of young adults [16]. The most common reason for trying e-cigarettes among adults is to reduce or quit cigarette smoking [17, 18]. The level of toxicant exposure from e-cigarettes is still not entirely understood, but most public health experts agree that *e-cigarettes deliver fewer toxicants than combustible cigarettes* [3-7, 12]. Thus, for smokers who try e-cigarettes, the health impact of use is dependent on whether they reduce or discontinue using cigarettes. For some users, e-cigarettes may facilitate a reduction or cessation in cigarette smoking [19-21]. However, most smokers who try e-cigarettes either abandon them completely after a short period or, more predominantly, engage in dual use [8, 10, 22]. We recognize the polarizing debate over e-cigarettes, with some emphasizing potential dangers [23-26], and others emphasizing potential benefits [27, 28]. We do not take a stance either way. Rather we argue that the impact (either benefits or harms) of e-cigarettes is strongly dependent on their uptake and ability to curb cigarette use. It is therefore important to understand the factors that lead to these different use patterns.

One obvious influence on e-cigarette adoption is the wide variability of both devices and e-liquids on the market. All e-cigarettes contain a lithium battery, a reservoir that contains e-liquid, and an atomizer that heats the e-liquid to create an aerosol that is delivered to the user. Beyond this basic structure, e-cigarettes vary on a wide range of dimensions including: concentration of nicotine in the e-liquid, flavoring, appearance, power, and ability for customization [11]. For current smokers who try e-cigarettes, these product characteristics affect their uptake by influencing the relative reinforcement value of e-cigarettes in comparison to cigarettes. Reinforcement value is well established as one of the primary determinants of tobacco use [29, 30].

A2. Product-level Determinants of E-cigarette Relative Reinforcement Value:

Figure 1 illustrates the conceptual framework by which product characteristics impact e-cigarette and cigarette use through relative reinforcement value. *Relative reinforcement value* is the perceived magnitude of a reward in comparison with the magnitude of competing rewards. Relative reinforcement value is sometimes quantified as the amount we would pay (i.e., value) for a given reinforcer when other reinforcers are also available. Estimates of this value are established measures of drug abuse liability, and have been utilized for making drug-related policy and regulatory decisions [31-34]. For drug reinforcers, reinforcement value has been shown to be strongly related to drug dose [35, 36]. For established users, reinforcement value can be maintained by sensorimotor cues that have been paired with drug delivery over many episodes of use, with these cues maintaining value even in the absence of drug delivery [37]. Thus, for established cigarette smokers who try a novel tobacco product, the two most important influences of reinforcement value are likely to be 1) nicotine delivery, and 2) sensorimotor cues (Figure 1).

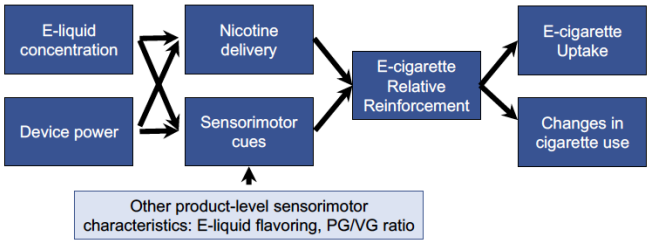


Figure 1: Product-level determinants of e-cigarette relative reinforcement value

Decades of research show that nicotine is the primary pharmacological reinforcer associated with tobacco use [13]. Nicotine dose is related to reinforcement value. In pre-clinical self-administration studies, higher doses of nicotine maintain higher rates of responding [38], and in human smokers, a reduction in the nicotine content of cigarettes reduces the reinforcement value of smoking [36]. We know less about how nicotine delivery relates to reinforcement value for e-cigarettes, but e-cigarettes can deliver as much or more nicotine as traditional cigarettes [39], and higher e-cigarette nicotine delivery has been shown to result in greater reductions in craving to smoke [40], greater reductions in withdrawal [40], and to impact uptake and smoking cessation [41]. In addition to providing effective nicotine delivery, e-cigarettes also offer potential to replace sensorimotor cues associated with smoking, which contrasts with many other non-cigarette tobacco products (and nicotine replacement products). Smokers have a long history in which sensorimotor cues (hand to mouth behavioral substitution, throat burn, warmth) are paired with smoking, and these cues can maintain behavior even when nicotine is absent [42, 43]. The “throat hit” associated with puffing a cigarette is related to nicotine delivery [44], and has long been considered to be important for the reinforcing effects of smoking [45, 46], and e-cigarette users consider it to be critical as well [47-49]. E-cigarettes also deliver a visible aerosol that is similar in appearance to cigarette smoke. E-cigarette users consider the temperature and volume of the aerosol to be an important sensorimotor characteristic [50, 51]. **Thus, both nicotine delivery and sensorimotor cues will determine relative reinforcement**, **and ultimately use of these products**. Both **nicotine delivery and sensorimotor cues are impacted by multiple product-level characteristics**, most critically 1) the **concentration of nicotine in the e-liquid** and 2) **how much power is delivered to the heating element** (Figure 1).

The concentration of nicotine in e-liquid (hereafter called concentration) varies from 0-50 mg/ml. Concentration is one of the primary determinants of nicotine delivery [52-55], and increases the "throat hit" associated with using an e-cigarette [56]. Likely as a result of its impact on nicotine delivery and sensory cues, concentration is an important factor in reducing smoking withdrawal [40, 57], and has been shown to impact uptake and smoking reductions [41]. But nicotine concentration is not the only determinant of reinforcement. *The power an e-cigarette device delivers to the heating element* is also an important determinant of both nicotine delivery and sensorimotor cues [51]. Higher power increases nicotine delivery [58], throat hit [15], aerosol volume [59], and aerosol temperature [51]. Some of the most advanced e-cigarettes (i.e., 3rd generation devices) allow the user to customize the power of the device, and have a range of power settings that extend much higher than devices with a lower, fixed power setting (i.e., 1st or 2nd generation devices). Later devices may better facilitate switching from cigarettes to e-cigarettes: users of high-powered 3rd generation devices are more likely to report abstinence from cigarettes [60], and to be former smokers [9]. This study will test the singular and combined effects of concentration and power by assigning participants to receive a low vs. high concentration and a low vs. high power in a 2x2 design.

Because nicotine delivery and sensorimotor characteristics are a joint function of e-liquid and device characteristics [61], smokers may choose products that produce the optimal nicotine delivery and sensorimotor stimulation. Thus, we expect (hypothesize) an interaction between concentration and power, and this becomes our **core scientific premise**. A higher-powered device that can deliver greater nicotine per puff of aerosol is likely to be more reinforcing when it is paired with a low nicotine concentration because this combination produces the optimal level of nicotine delivery. Low nicotine concentrations paired with low power may not deliver enough nicotine or provide enough sensorimotor stimulation to be reinforcing, while high nicotine concentrations paired with high power may provide aversive levels of nicotine or an aversive throat hit. Consistent with this prediction, a small study of 20 e-cigarette users found that users of higher powered devices used lower e-liquid nicotine concentrations than users of lower-powered devices, but obtained higher levels of plasma nicotine [62]. Furthermore, a recent survey of 436 current e-cigarette users found a strong negative relationship between the power of device settings and user's chosen e-liquid nicotine concentration ($r = -0.44$) [14]. In one experimental lab study, smokers reported that a lower concentration was required to produce the optimal throat hit when using a higher power setting [15]. However, we also know that e-cigarette users can compensate for changes in these characteristics by modifying their puffing behavior [59, 61]. When device power or nicotine concentration are lower, e-cigarette users have been shown to take longer puffs, more puffs, and ultimately consume more e-liquid [59, 61] Thus, an alternative hypothesis is that that these characteristics may be relatively unimportant, as long as users are able to modify their behavior in order to achieve the desired effect. The interactive effects of concentration and power remain unclear, and serve as the central focus of this application.

A3. Significance for Tobacco Regulation:

This research has implications for tobacco regulation. The US FDA recently deemed e-cigarettes to be under their regulatory authority, thus allowing the FDA to set product standards as needed for the protection of public health[63]. The proposed research project will provide information about two critical e-cigarette characteristics, concentration and power, and how they impact use and ultimately health outcomes, forming the scientific basis for future tobacco regulation. Indeed, a recent report from the **National Academy of Sciences, Engineering, and Medicine listed "trials comparing e-cigarettes with different product characteristics on [use] outcomes to inform product standards" as a top priority for research [12].**

A4. Impact of Individual Differences on Product Preferences:

We recognize that individual characteristics are likely to influence the relative reinforcement value of two or more tobacco products (e.g., age, gender, race, dependence, socioeconomic status, motivation to quit). We plan to recruit participants that vary on these characteristics, and will have the opportunity to conduct exploratory tests of their impact. Any individual factors that are judged to be of importance based on these exploratory analyses will become a larger focus in the planned R01 submission in Year 2. Another critical individual-level factor is prior e-cigarette experience. Experienced e-cigarette users obtain greater nicotine delivery from the same device and e-liquid than e-cigarette naïve current smokers [64], primarily through longer puff duration [65], and this change takes place within the first week of use [66]. In this study, we will limit the sample to cigarette smokers with limited e-cigarette experience, thereby methodologically constraining this variance. Nonetheless, we expect that there may be changes in nicotine delivery that result in changes in reinforcement value and use across the three-week sampling period. We will include sampling week as a variable in all analyses (described below).

A5. Other Device and Sensory Characteristics:

We focus herein on those characteristics that are the largest determinants of nicotine delivery (device power & nicotine concentration). However, other product characteristics are also important. First, e-liquid is available

in nearly 8000 flavorings [67]. Flavors have been reported as a common reason for using e-cigarettes [68-70], especially among young adults and adolescents [71]. An experimental test of different flavors would require many groups (flavors), which we do not believe is feasible or wise for a K application, especially given other ongoing studies with this focus [72-75]. In the present study, we model the current marketplace by providing participants with a choice of e-liquid flavors from which to choose (and can use this as a potential covariate if needed). Second, the base constituents in e-liquid, both propylene glycol (PG) and vegetable glycerin (VG), come in a range of PG/VG ratios. PG/VG ratio has been reported as an important determinant of the sensorimotor characteristics described above [76], although likely less so than concentration and power.

B. Innovation

The present study is innovative in at least four ways. First, prior e-cigarette research has primarily focused on the impact of e-cigarettes as a class of products on uptake and cigarette smoking, without attending to the impact of specific product features. These product features are critical factors about which we know very little. While a small subset of studies are underway to understand the impact of e-liquid nicotine concentration on reinforcement and use [78, 79], no studies assess the impact of device power or how device power interacts with nicotine concentration to affect reinforcement value and tobacco use patterns. Second, this will be one of the first studies to use an experimental design to test the impact of product characteristics. Many published or ongoing studies measure and report the characteristics of e-cigarettes being used in the population (i.e., observational research) [80-83], including the Population Assessment of Tobacco and Health (PATH). These studies are informative about the use of products with different characteristics. However, a strength of the present study is that it is naturalistic, but randomized in nature, allowing us to draw stronger conclusions about the impact of these characteristics. Third, unlike PATH, we embed more frequent (i.e., granular) assessment of use outcomes. Participants complete electronic diaries that provide daily measures of smoking behavior, and the e-cigarette device collects detailed and objective information about e-cigarette use including puff duration and puff number. Fourth, the present study takes a more comprehensive approach to understanding influences on relative reinforcement than previous studies by measuring individual-level factors to be included in exploratory moderation analyses.

C. Approach

C1. Design Overview (Figure 2):

Adult smokers (21+ years) will be provided with an e-cigarette device and e-liquid (described below) to sample over a three-week period. Participants will be blind to nicotine concentration and device power, which will be varied in a 2x2 between-subjects design. We will not directly manipulate e-liquid flavor, but to mimic real-world e-cigarette use, all participants will be given a choice of three flavorings, and flavor choice will be included as a covariate if necessary. Participants will be told to use the e-cigarettes as much or as little as they wish. During the sampling period, we will assess daily use of cigarettes via electronically delivered diaries, and use of e-cigarettes throughout the sampling period will be recorded by the e-cigarette device. At randomization and at the end of the sampling period, participants will complete a laboratory-based choice procedure to assess the relative reinforcement value of the two products. A final follow-up will occur 1 month after completion of sampling phase to determine how the characteristics of the product sampled may have impacted likelihood of purchasing an e-cigarette, characteristics of the e-cigarette purchased, and tobacco use during follow up.

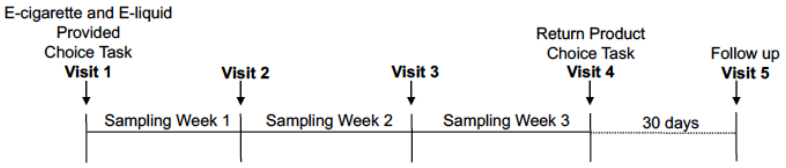


Figure 2: Schematic of study design

C2. Other Design Considerations:

First, we considered including adolescents, an important population in regards to e-cigarette use. However, the critical question for adolescents relates to whether e-cigarette use in naïve individuals causes downstream cigarette use, a very different research question than the one proposed here. Second, we considered a test of second vs. third generation e-cigarette devices given that these classes of products are highly prominent on the marketplace, but were concerned that a design of this nature would confound device power with the ability to modify the device, as is the case for third (but not 2nd) generation devices, and would not allow us to isolate the impact of power. Finally, we recognize that in our design e-cigarettes are provided for free while participants continue to pay for their usual brand cigarettes. However, this inequity exists for all groups such that if it inflates e-cigarette use, it is not confounded with product characteristics. Measures of demand are also included at the end of sampling to estimate e-cigarette use at a variety of prices.

C3. Participants:

Daily cigarette smokers (n=200) will be recruited from the local community using standard media outlets. We will also submit a Research Data Request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The study team will not cold-contact any patients who have opted out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. We will reach out to these potential participants via MyChart message, text message, phone call, or email no more than three times via any one contact method. Although we anticipate having 180 participants complete the study, here we have increased this sample size to 200 in anticipation of attrition. We will recruit an equal number of young adult (21-30) and older adult smokers (>30) to allow for exploratory analysis on the impact of age. In/exclusion criteria are designed to enroll relatively healthy smokers who predominately use cigarettes and have limited experience with e-cigarettes. Inclusion criteria include a) adults who have been smoking at least five cigarettes daily for the past year (baseline CO > 8ppm), b) rate their interest in using e-cigarettes as >5 on a 0-10 scale, c) have a smartphone that can receive text messages and has access to the internet or has an e-mail account they check daily and d) must be age 21 or older. Exclusion criteria include a) use of tobacco products other than cigarettes, including e-cigarettes, on ten or more days in the past 30 days, b) current use of cessation medications, c) pregnant, trying to become pregnant, or breastfeeding, d) recent history of cardiovascular distress in the last three months (e.g., arrhythmia, heart attack, stroke, uncontrolled hypertension), e) history of a seizure disorder, f) household member currently enrolled in the study.

C4. E-cigarettes and E-liquids:

E-cigarette device will be chosen based on the following guiding principles: 1) can deliver power in the desired range (20W, 40W), 2) can be fixed at those settings by experimenters, but not easily altered by participants, and 3) is able to provide objective measurement of e-cigarette use. We are aware of at least one device that meets these criteria: Evolv DNA 75c Color with Tobacco Mini Tank. We will utilize eScribe software, available specifically for researchers for the Evolv device, which allows experimenters to fix the device settings such that they cannot be altered by participants, and can blind the participants to the power settings. This software can also retrieve information about the participant's use of the product including the number of puffs, the puff duration, and the puff volume, which we view as a great strength. If this device becomes unavailable, we will choose another e-cigarette device using the same principles, and expect that the proliferation of devices will add to our list of options from which to choose.

Nicotine concentrations will be 3 vs. 12 mg/ml, chosen based on preliminary data from Dr. Wagener's (co-mentor) trials showing these are the most popular concentrations for devices with wattages in the range used here. The high nicotine concentration is in a range that has been shown to deliver cigarette-levels of nicotine in naïve users assigned to a low-powered device (12-36 mg/ml) [55], and similar concentrations are currently being used in other e-cigarette clinical trials [78, 79]. However, the low concentration is in the range shown to be popular with higher-powered devices (3-6 mg/ml) [84]. The e-cigarette device and atomizer will be constant for all participants, but will be fixed at a low (20 W) or a high (40 W) power using the eScribe software described above. The lower power setting was chosen to be in a similar range to popular low-power, second-generation devices [55]. The high-power setting was chosen to be in a range of available settings for popular third-generation devices and based on preliminary data from Dr. Wagener's lab showing it delivers cigarette-levels of nicotine at 3 mg/ml concentration with a typical e-cigarette puff duration (3.4 s, 0.1 mg nicotine / puff, unpublished data).

We recognize that multiple device characteristics contribute to changes in power including battery voltage, coil resistance, and coil size [85]. The device chosen here manipulates power via changes in the voltage of the battery, holding other features constant. This design has strong internal validity because only one aspect of the device is changing. Although voltage is being manipulated here, we view the results as having implications for all of the determinants of power described above.

E-liquid will be purchased from American E-liquid, which has been used in other research studies [86] and is available in a wide range of concentrations and flavors. E-liquid flavors will be chosen based on the three most popular flavors at the time of study onset.

C5. Procedures:

C5a. Screening, Baseline, and Randomization (Visit 1): Potential participants will be phone screened for initial eligibility. Alternatively, participants may complete a Redcap survey to determine initial eligibility. Participants will see a script that briefly explains the study. Those meeting criteria will either by consented electronically or consented at an in-person visit. Consented participants will attend an in-person visit where they complete additional baseline measures and provide a urine sample for cotinine analysis. We will provide transportation via a taxi cab company for participants who are eligible, but do not have reliable transportation to in-person visits. All participants will receive an e-cigarette and e-liquid, varying in 2x2 manner on both nicotine concentration (3 vs. 12 mg/ml) and power (20W vs 40W) (n=45cell). Participants will be given instructions

about how to fill and operate their device, similar to what might be conveyed online or in a vape shop. Participants will be told to use the e-cigarette as much as they would like, and that they are not required to use the e-cigarette or to smoke cigarettes, but we request that they do not use any non-study e-cigarettes during this time period (to avoid use of products with different characteristics than those assigned). We are forced to rely on self-report of non-study e-cigarette use, but we do not expect it to be a pervasive problem given that current e-cigarette users are excluded, and because we provide product for free. Both participants and research staff will be blind to assigned nicotine concentration and power settings. At each visit, participants will be provided with a one-week supply of e-liquid such that they could exclusively use the e-cigarette if they choose to do so. Participants will also complete a lab-based preference assessment (described below).

C5b. Sampling (Visits 2-4): We considered a longer sampling period but our experience in prior sampling studies is that 3 weeks is sufficient to acclimate [77]. Over the three-week sampling period, participants will complete daily electronic diaries cataloging their cigarette and e-cigarette use. Each morning, participants will receive an e-mail or text message link to complete their diary. The diary will assess tobacco use the previous day including cigarette smoking, number of e-cigarette puffs per day, quit attempts, and craving. This electronic daily diary is currently being used in Dr. Carpenter's R01 and Dr. Smith's pilot study, with compliance > 90%. Participants will attend weekly in-person visits where they will complete assessments regarding tobacco use, craving, dependence, product perceptions, as well as provide expired carbon monoxide samples. Urine samples for cotinine analysis will be provided at randomization and at the end of sampling. Research staff will conduct routine device maintenance at these visits. At the end of the sampling period (Visit 4), participants will return their e-cigarette device and e-liquid, and complete the preference assessment again.

C5d. Follow-up (Visit 5): Participants will return to the lab one month following the end of the study to assess their cigarette smoking, e-cigarette use, e-cigarette purchases, and provide expired breath carbon monoxide.

C5e. Modified Procedures to be Implemented During COVID-19 Restrictions: After passing initial screening, all participants will be consented into the study through our established remote procedures, instead of having the option to complete the consent process in person. All in-person screening questionnaires that can be administered over the phone prior to the visit will be completed over the phone (demographics questionnaire, physiological & medical history, & tobacco use history). Participants who are ineligible based on these questionnaires will be paid for the visit, but not required to come in to the lab to complete the remaining screening assessments. If the participant is still eligible after completing these questionnaires, we will then schedule them to come into the laboratory to complete the remainder of the visit. For visits 2-5, we will complete any questionnaires remotely that we can complete remotely. For interview-administered questionnaires, we will call participants in advance of the visit and complete the questionnaire over the phone via interview with study staff. For questionnaires that are completed independently by the participant, we will send them a RedCAP link prior to the visit and request that they complete the questionnaires on their own. If participants fail to complete these questionnaires on their own or we are unable to reach them to complete the questionnaires, we will ask the participant to complete them at the visit in the lab.

Participants will be called 24 hours prior to all visits to confirm they are not experiencing any symptoms of COVID-19. All participants for each visit will be required to wear a mask and remain six feet away from the research staff and others when possible. When staff and participants must interact (for CO collection and e-cigarette disbursal), at least six feet of distance will be maintained by placing materials on a desk/table six feet away from the participant and then staff stepping away while the participant approaches to retrieve materials. All surfaces will be sanitized prior to the visit and after the visit.

C6. Compensation:

Participants will receive $25 for Visits 1 and 4 (1.5 hours), $15 for Visits 2, 3, and 5 (45 minutes), and a $75 completion bonus if they complete all visits. Participants can earn additional payment for daily diaries based on # completed (up to $25/week). Participants who attend all sessions and complete all diary entries could earn $245.

C7. Measures

Table 1. Study Measures	**V1 (SCR/BSL)**	**V2**	**V3**	**V4**	**V5 (FU)**
Screening Assessments					
Demographics, Medical, Tobacco, Drug, & Alcohol Hx	X				
Measures of relative reinforcement and dependence					
Purchase Tasks	X			X	X
Preference Assessment	X			X	

Dependence (FTND/WISDM/Penn State)	X			X	X
Measures of smoking behavior					
Daily Diaries	Start	-----	-----	End	
Detailed measures of e-cig use collected from device	Start	-----	-----	End	
Timeline follow back		X	X	X	
Follow-up tobacco use questionnaire					X
Measures of nicotine delivery and sensorimotor cues					
Urinary cotinine (Nicotine Exposure)	X	X		X	
Withdrawal / Craving (MNWS/QSU)	X	X		X	
Sensorimotor items added to mCEQ	X	X	X	X	
Other self-report questionnaires					
Product Satisfaction (mCEQ)	X	X		X	
Perceived Health Risks	X	X		X	
Adverse Event Assessment		X	X	X	X
Physiological Assessments					
Carbon Monoxide (Smoke Exposure)	X	X	X	X	X

C7a. Screening Assessments: Preliminary eligibility will be determined on the phone before participants are either consented electronically or invited for an in-person visit to provide consent. Alternatively, participants may complete a Redcap survey to determine initial eligibility. Participants will see a script that briefly explains the study.Consented participants will attend an in-person visit where they complete screening questionnaires related to demographics, tobacco use history, and expired carbon monoxide. During the COVID-19 restrictions, all consenting will be done remotely.

C7b. Measures of Relative Reinforcement and Dependence: Relative reinforcement will primarily be assessed using a lab-based preference assessment, a well-validated measure of reinforcement value [(88)]. First, participants will sample their usual brand cigarette to standardize time since last cigarette. Then participants will sample their assigned e-cigarette and e-liquid. Immediately after sampling each product, participants will complete questionnaires about that product, including a modified version of the mCEQ [(89)], a perceived health risk measure, and a purchase task. Then, participants will complete the preference assessment in which over a period of 30-minutes and 10 trials (three-minute inter-trial interval), participants choose between taking two puffs of the e-cigarette, two puffs of their usual (own) brand cigarette, or abstaining from both. This task measures the impact of concentration and power on changes in the relatively reinforcement value of smoking compared to using the e-cigarette. The primary outcome is the number of choices to smoke the usual brand cigarette, but secondary outcomes include the number of choices to use the e-cigarette and to abstain. We considered utilizing a cigarette other than the participant's usual brand to control for novelty, but changes in relative reinforcement value of the participants' usual brand cigarette are most relevant from a public health perspective. Our lab space includes ventilated smoking rooms equipped with cameras and intercom, which allow us to guide participants through the task from a separate area. A secondary measure of reinforcement value will be the purchase tasks—hypothetical tasks in which participants estimate the intensity with which they would use cigarettes and e-cigarettes at a variety of prices [(90, 91)]. An individual's sensitivity to the cost of a tobacco product is considered to be an estimate of that product's reinforcement value [(31)]. Dependence will be assessed at in-person visits using established measures of cigarette and e-cigarette dependence (Fagerstrom Test for Nicotine Dependence [(92)], Wisconsin Inventory of Smoking Dependence Motives [(93)], Penn State E-cigarette/Cigarette Dependence Scale [(94)]). Dr. Smith is utilizing both the preference task and the demand measures in her ongoing pilot trial focused on PG/VG ratio in e-liquids.

C7c. Measures of tobacco use: Daily cigarette use will be captured using an electronic daily diary in which participants report the number of cigarettes they smoked (< 2 min/day). We will collect expired breath carbon monoxide at each weekly visit, which provides an objective measure of recent exposure to smoke, but is unaffected by e-cigarette aerosol. During weekly assessments, we will retrieve information about e-cigarette use from the device, using eScribe software described above. The software provides the number of puffs taken each day and the average puff duration. Within weekly lab visits, participants will retrospectively report these outcomes via timeline followback.

C7d. Measures of Nicotine Delivery: Participants will provide urine samples for testing of cotinine (primary metabolite of nicotine) within our Departmental lab. We will not be able to discriminate the source of nicotine

(cigarette vs. e-cigarette), but will be able to test whether overall nicotine exposure has increased or decreased from baseline. We will also measure the quantity of nicotine liquid that participants use by weighing the e-liquid bottles at distribution and at each visit, which combined with the concentration provides some information about nicotine intake from the assigned e-cigarette. We will also assess subjective assessments of nicotine effects including withdrawal (MNWS [95]), and craving to smoke (QSU [96]).

C7e. Measures of Sensorimotor Cues: Because e-cigarettes are relatively new products, there are no validated measures to assess reinforcement from sensorimotor cues. In consultation with Dr. Wagener (co-mentor) we will include items that assess participant satisfaction with throat hit, aerosol volume, aerosol temperature, and flavor. These items will be added to a modified version of the mCEQ [89], which will assess reward and satisfaction from both cigarettes and e-cigarettes.

C8. Statistical Considerations:

Power analysis was completed for the primary outcome of percentage reduction in average cigarettes per day smoked in the last week of sampling, and based on data from Dr. Carpenter's previous e-cigarette sampling trial during which participants received a low power (1st Gen) device with one of two nicotine concentrations (low or high) [84]. We hypothesize that the impact of nicotine concentration on CPD reduction would be similar here for the low power groups and that the effect would reversed, but of similar size, in the high-power groups (Figure 3a). The hypothesized interaction is shown during the last week of sampling for simplicity in Figure 3b, specifically that for the low power setting, a higher concentration will produce a larger decrease in cigarettes per day than the low concentration, but for the high-power setting, a higher concentration will produce a smaller decrease in cigarettes per day than the low concentration. We use the methods described by Fleiss[104] for estimating power for interaction effects. As he notes, the variance of an interaction effect is four times that of the corresponding main effect. Thus, even large effects require large sample sizes to yield adequate power. In this case, a sample size of 40 participants / group will provide 80% power to detect an interaction among the two factors with a 0.050 significance level, assuming that the common standard deviation is 38% reduction in CPD, as was the case in Dr. Carpenter's trial [84]. However, we inflate this sample size by 10%, accounting for attrition over time, and thus aim to **recruit 45 participants randomized per group (total N=180).**

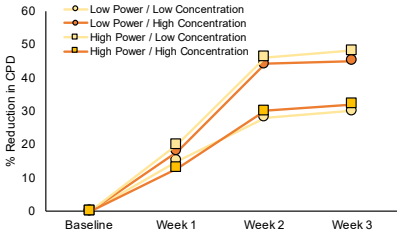


Figure 3a: Hypothetical Changes in CPD over sampling

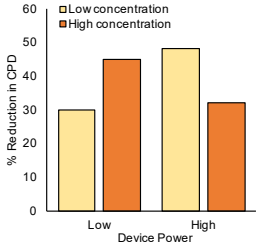


Figure 3b: Impact on reduction in CPD

For aims 1 and 2, we will assess the impact of concentration and power on each outcome across time using a generalized estimating equation that includes concentration, power, sampling week (time), and their interactions. Hypothesis 1 will focus on percentage reduction in CPD, Hypothesis 2 will focus on e-cigarette uptake (puffs per day), and Hypothesis 3 will focus on complementary measures of preference/demand, all of which are captured at Visit 4. Outcomes that are skewed (e.g., demand parameters, urinary cotinine) will be log transformed. It is possible that reductions in CPD will be bimodal in the last week of sampling, reflecting a subset of participants who may quit smoking during the trial. In this case, we would conduct a Chi-square test on the proportion of participants who reduce their smoking by at least 50%. Exploratory analyses on age will be conducted by adding age to the model. Dr. Elizabeth Hill (co-mentor) will be meeting with Dr. Smith monthly for training in these analyses, and will also be available to assist with the eventual power analysis for the R01 submission based on these data.

Protection of res

1. Risks to Human Subjects

1.1 Human Subjects Involvement, Characteristics, and Design:

Current smokers (n=180) will be randomly assigned to one of four research groups in a 2X2 between-subjects design. All participants will receive an e-cigarette and e-liquid to sample over a three-week period. The e-liquid will either have a low or a high nicotine concentration, and the e-cigarette will either have a low or a high-power setting. Group assignment will be double-blind, and 15 participants will be randomized to each group.

1.2 Study Procedures, Materials, and Potential Risks:

Study Procedures:

Participants will be screened over the phone to determine initial eligibility. Altneratively, participants may complete a redcap survey to determine initial eligibility. Participants will see a script that briefly explains the study. Once participants have been determined to be initially eligible, they will be invited to participate in the consent process. The consent process will take place via one of the following modalities: 1) Remote electronic

consent (e-consent) via REDCap facilitated with a discussion over the phone, 2) Remote consent via doxy.me, or 3) in-person consent (in-person visit at start of Visit 1). During the COVID-19 restrictions, all consenting will be done remotely (not in-person). We have built in the option for electronic consent to reduce the length of the first in-person visit and while still providing ample time for the consent process. Consented participants will be asked to attend an in-person screening session. Participants will be asked to provide a carbon monoxide sample to confirm smoking status, and women will provide a urine sample for pregnancy testing. Participants will then complete a series of interview-administered and participant-administered questionnaires that assess brief medical history, tobacco use history including prior and current e-cigarette and cigarette use, current use of smoking cessation products, and demographics. After all questionnaires have been completed, study staff will determine participant eligibility.

Participants who are eligible will then provide a urine sample for cotinine analysis and complete additional baseline questionnaires including measures of nicotine dependence. Participants will be randomized to one of four groups as described above and will have the opportunity to sample their usual brand cigarette and their assigned e-cigarette and e-liquid for the first time. After sampling each product, participants will complete additional questionnaires and complete the preference assessment where they choose between their cigarette and assigned e-cigarette. At the end of Visit 1, participants will receive a one week supply of e-liquid to take home with their assigned e-cigarette, will be enrolled in the daily electronic diary system, and will be provided with instructions for completing diaries.

Participants will return to the lab for three additional weekly visits, and will receive a new supply of e-liquid for each week. At each visit, we will assess tobacco use during the prior week, participants will provide an expired breath carbon monoxide sample, adverse events will be assessed, and participants will complete questionnaires about their assigned e-cigarette and e-liquid. At the fourth and final weekly visit, participants will complete the sampling and preference assessment again, providing another rurine sample for cotinine testing, and return any unused study product.

Materials:

Research material obtained from the participants include responses to questionnaires collected directly by our research team and entered directly within secure databases. Data will be stored in a password protected redcap database and on password protected network storage. Consent forms will be stored in a separate locked filing cabinet or electronically on Redcap or a secure Box account. Physiological measures include: urine collected for pregnancy testing, as well as expired breath carbon monoxide. Research data will be obtained specifically for research purposes. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA. For participants recruited from the MUSC EHR, the recruitment project will also be housed in REDCap and only CITI and IRB certified personnel will have access to the database. The research team will only have access to the REDCap recruitment project while actively enrolling participants for the study. The recruitment project will be stored separately from the other study REDCap projects.

Potential Risks:

The research protocol calls for smokers to use e-cigarettes in the lab and (if they desire) at home. E-cigarettes are no more harmful than conventional cigarettes, and various studies suggest that they may offer reduced harm. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants.
Potential risks are as follows:

E-Cigarettes

E-Cigarettes are not combusted, and therefore levels of carcinogens are markedly reduced, if not eliminated, comparable to trace levels seen in nicotine replacement products [(97)]. E-liquid will contain propylene glycol, which some suggest may be harmful. Propylene glycol is an FDA approved food additive, but with uncertain effects upon inhalation.

As for adverse events, the majority of e-cigarette studies are based within on-line surveys. We report here on three moderate to large such surveys. In the first [(98)], three side effects were reported by >20% of respondents: headaches (21%), cough (27%), and increased phlegm (25%). In the second [(99)], the most common negative effect of e-cigarette use was throat and mouth irritation, and fewer than 3% “reported a high level of side effects.” Finally, the largest online survey to date [(100)] did not fully assess adverse events, but reported that 26% of e-cigarette users reported burning in throat. In a cross-over study of 40 smokers given e-cigarette for four days [(101)], the four most common adverse events (within highest dosage group) were

mouth/throat irritation (38%), nausea (29%), vertigo (21%) and headache (22%). All other adverse events were rare (<5%).

In the recent RCT from New Zealand [102], there was a higher number and proportion of adverse events among active e-cigarette group, but the event rate did not significantly differ as compared to nicotine patches. In the RCT from Italy [103] there was no differential rate of adverse events among high, medium, or placebo e-cigarette groups. The five most common adverse events were dry cough, mouth irritation, shortness of breath, throat irritation, and headache, with no serious adverse events. The study also reported no significant changes in body weight, resting heart rate, or blood pressure.

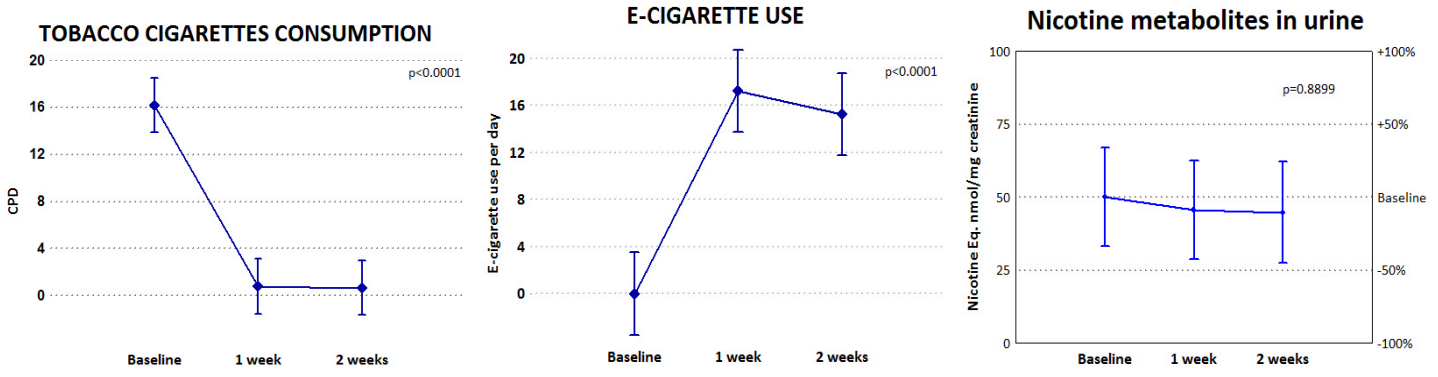
There have been a small number of reports to the FDA of people using e-cigarettes and experiencing seizures, with most reports involving youth or young adult users. This is rare and will be monitored. We have added an exclusionary criteria for history of seizure disorder.

There have been a number of reports of respiratory illness, and even some deaths from that respiratory illness, among individuals using e-devices. No specific substance or product has been linked to these cases. Many of but not all of the cases involved users vaping THC, the active ingredient in marijuana. Some of the instances are specific to nicotine alone. We advise all participants not to add any substances to the devices we give them. We advise against using any e-device or e-liquid that is obtained by questionable or unknown sources (such as off the street or on the black market). While we believe that e-cigarettes are less harmful for adult smokers than regular cigarettes on a long-term basis, there may still be short term risks of using e-cigarettes. We will continue to monitor your health in our study by asking you at every study contact a set of specific questions about any changes you have experienced since the last study contact.

Concurrent use of e-cigarettes and smoking

If smokers engage in dual use, the major concern will be too much nicotine intake. Symptoms of nicotine intoxication include nausea, dizziness, headache, and stomachache [104]. In Dr. Carpenter's two prior studies, wherein participants who used nicotine gum/lozenge and smoked concurrently, there was no evidence of nicotine intoxication [105, 106], nor have we seen serious adverse events in our current e-cigarette studies. We recently completed a literature review [107] that showed combined NRT, as well as concurrent use of NRT and smoking, were both safe.

A recently completed short-term observational study included 20 smokers who were provided e-cigarettes for ad libitum use over a 2-week period. Data below demonstrate that changes (increases) in e-cigarette use increased in direct proportion with changes (decreases) in cigarette smoked (1st and 2nd panel), resulting in no net change in nicotine (3rd panel). Thus, smokers who engage in dual use are likely to NOT increase total nicotine intake, a finding replicated elsewhere [108]. These findings are very much consistent with Dr. Carpenter's prior work on smokeless tobacco, wherein smokers were provided with snus to use ad libitum over two weeks, finding no net increase in nicotine intake.



Undermining Cessation

Another potential risk is that the sampling intervention will decrease rather than increase future cessation. We are aware of one recent longitudinal study [109] that showed numerically lower but still statistically similar rates of non-smoking among e-cigarette users vs. non-users, but this study did not assess for timing of e-cigarette use. This is the only study to show this that we are aware of. However, most of the available data available suggest that e-cigarettes either do not affect cessation or increase it [98, 100, 102, 103, 110-112].

Use of E-cigarettes among non-participants and non-smokers, including children

Whenever a product is given to a smoker to take home and use, there is potential that the product will be used by someone else, inclusive of non-smokers and even children. In Dr. Carpenter's recently completed snus trial in which he mailed tins of smokeless tobacco to smokers all over the country, such "diversion" was not a problem. We will advise participants who receive e-cigarettes to keep them out of reach of children and pets.

Confidentiality

A final risk is breach of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Informed Consent:

All research personnel have up to date CITI Certification for Protection of Human Subjects, and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets (e.g., craigslist, flyers, print ads, facebook). Those who call expressing interest in study participation will be screened for an initial eligibility determination. We will also submit a Research Data Request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The study team will not cold-contact any patients who have opted out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment. We will reach out to these potential participants via MyChart message, text message, phone call, or email no more than three times via any one contact method. Once initial elgibility has been determined, the consent process will be initiated. The consent process will take place via one of the following modalities: 1) Remote electronic consent (e-consent) via REDCap facilitated with a discussion over the phone, 2) Remote consent via doxy.me, or 3) in-person consent (in-person visit at start of Visit 1). We have built in the option for electronic consent to reduce the length of the first in-person visit and while still providing ample time for the consent process. All participants will be provided with a hard copy and/or electronic copy of the consent form . Participants will be given time to review the consent documents, as well as a detailed overview of the consent documents by study staff. After participants have read the documents and the documents have been described by the study staff, participants will demonstrate that they understand key aspects of the study by verbally answering questions from study staff about participation (e.g., "Can you tell me what the risks of participation are?"). Participants will sign the consent form only after both the participant and the study staff member are confident that the participant understands their participation and the risks associated with participating. Consent signatures may be collected on paper or electronically. When consent is collected electronically, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap/Box folder if captured electronically. The HIPAA form can be signed on paper or electronically. For the electronic process, all pages of the approved HIPAA document will be uploaded into REDCap for review by the participant. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Each participant will still receive a paper copy of the "Notice of Privacy Practices" and each signed HIPAA can be downloaded from REDCap as a PDF. These procedures will be done on our research team's combination laptop/tablet, but no data will be stored on the laptop/tablet; all data will be stored securely in Redcap/secure Box folder. Only those participants who provide consent will complete the additional screening questionnaires. Additional screening measures include additional questionnaires, an expired carbon monoxide sample to confirm smoking status, and (if female) a urine pregnancy test. Participants who are deemed eligible at that point will then complete additional baseline questionnaires. On all correspondence with potential participants, we provide our toll-free number if any questions or problems arise. We will abide by all HIPAA regulations as set forth by our institution. Dr. Smith will supervise all aspects of the recruiting process.

2.2 Protection Against Risk:

Use of E-cigarettes

Participants will be screened for general medical precautions (pregnancy, cardiovascular disease), and all participants will be monitored for adverse events during the study period. We will clearly advise against use of e-cigarettes during pregnancy and breast-feeding and will verify non-pregnancy at study onset. Participants will be educated about potential risks of e-cigarette use, including concurrent use with cigarettes. Any adverse events will be reported to the IRB. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (~5%) and mild (mouth/throat irritation, headache, nausea, headache), and will be handled quickly (i.e., advice to participant to reduce or stop e-cigarettes). Lab studies of toxin exposure (above) suggest that e-cigarettes confer no greater risk to health than do conventional cigarettes. It is unlikely that e-cigarette users will

become addicted to the product in the 3-week sampling period. All participants will be provided with cessation information (referrals to Quitline) as part of this study. Dr. Kevin Gray has agreed to serve as the study medical advisor. Both Dr. Smith and Dr. Carpenter have worked with Dr. Gray in the capacity before, and Dr. Gray will be available as needed for consultation on study eligibility criteria or adverse events.

Concurrent Use of E-cigarettes & Smoking

Per above, the most common effects from too much nicotine are nausea, headache, and disturbed sleep. The sampling period is three weeks in duration, and thus we do not expect sustained patterns of dual use. We will track adverse events at every study contact, and will have a toll-free number available for participants to call if they experience an adverse event (AE). All study contacts will remind participants of this number. Participants will be encouraged to contact study staff as soon as possible for serious events. If they wish, they may contact their local MD or give the study medical advisor permission to do so. We will withdraw participants who have a serious AE, become pregnant or begin breast-feeding. For other AEs, if the study medical advisor (Dr. Kevin Gray), the participant's physician or the participant wishes it, the participant will be withdrawn from the study.

Undermining Cessation

We emphasize that this is not a cessation trial, though we will collect various cessation outcomes. Nonetheless, it is possible that use of e-cigarettes will undermine quitting (though this would be contrary to existing literature). At the end of the study, participants will be advised to stop using all tobacco products, including e-cigarettes.

Diversion of e-cigarettes

We will strongly advise participants that they are not to share the study product with others, and that they should store the product in a secure area that is out of reach of children and pets. We cannot directly assess any diversion/uptake from the perspective of adolescents, since that would require separate consent, and is a separate research question.

Confidentiality

We will use the participant's name only on the screening and informed consent documents and these will be kept in a locked file, to be kept centrally at our study office, or electronically in Redcap. Copies of informed consent will be kept by research personnel under lock and key, or on recap when collected electronically. When consent is collected electronically, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap if captured electronically. The HIPAA form can be signed on paper or electronically. For the electronic process, all pages of the approved HIPAA document will be uploaded into REDCap, using a SCTR-developed template and procedures, for review by the participant. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Each participant will still receive a paper copy of the "Notice of Privacy Practices" and each signed HIPAA can be downloaded from REDCap as a PDF. These procedures will be done on our research team's combination laptop/tablet, but no data will be stored on the laptop/tablet; all data will be stored securely in REDCap.

The research materials will become part of the modern record keeping facility of the Institute of Psychiatry, which will minimize risks to the privacy of participants. All interviews, records, charts, rating scales, and other patient information will be kept in locked files at the Cancer Control Program, with limited access to the study personnel. All database files will include password protection to further ensure confidentiality.

3. Potential Benefits of the Proposed Research to the Participants and Others

This study is not likely to offer any direct benefit to the participants in the study.

4. Importance of the Knowledge to be Gained

In an ever-changing marketplace of tobacco-produces and nicotine-delivery devices, e-cigarettes are arguably the most popular new products available to smokers. The most important question about e-cigarettes is whether it will have a positive or negative impact on public health. The impact on public health is largely dependent on whether e-cigarettes reduce combustible cigarette use. This study will provide information about whether one e-liquid characteristic will impact reinforcement value of e-cigarettes among current combustible cigarette users.

Statistical Analysis Plan

Power analysis was completed for the primary outcome of percentage reduction in average cigarettes per day smoked in the last week of sampling, and based on data from Dr. Carpenter's previous e-cigarette sampling trial during which participants received a low power (1st Gen) device with one of two nicotine concentrations (low or high) [84]. We hypothesize that the impact of nicotine concentration on CPD reduction would be similar here for the low power groups and that the effect would reversed, but of similar size, in the high-power groups. In this case, a sample size of 40 participants / group will provide 80% power to detect an interaction among the two factors with a 0.050 significance level, assuming that the common standard deviation is 38% reduction in CPD, as was the case in Dr. Carpenter's trial [84]. However, we inflate this sample size by 10%, accounting for attrition over time, and thus aim to **recruit 45 participants randomized per group (total N=180).**

For aims 1 and 2, we will assess the impact of concentration and power on each outcome across time using a generalized estimating equation that includes concentration, power, sampling week (time), and their interactions. Hypothesis 1 will focus on percentage reduction in CPD, Hypothesis 2 will focus on e-cigarette uptake (puffs per day), and Hypothesis 3 will focus on complementary measures of preference/demand, all of which are captured at Visit 4. Outcomes that are skewed (e.g., demand parameters, urinary cotinine) will be log transformed. It is possible that reductions in CPD will be bimodal in the last week of sampling, reflecting a subset of participants who may quit smoking during the trial. In this case, we would conduct a Chi-square test on the proportion of participants who reduce their smoking by at least 50%. Exploratory analyses on age will be conducted by adding age to the model. As described in the Career Development Plan, Dr. Elizabeth Hill (co-mentor) will be meeting with Dr. Smith monthly for training in these analyses, and will also be available to assist with any unexpected issues. Gender will be examined separately as a direct or moderating influence on all outcomes.

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