Comparison of Leading E-cigarette Product Types on Relative Reinforcement Value and Tobacco Use Patterns Among Current Smokers

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ABSTRACT

Some smokers who try e-cigarettes transition completely from cigarettes to e-cigarettes, but others continue to use both products, or abandon e-cigarettes and return completely to cigarettes. One factor that likely impacts these tobacco use patterns is the e-cigarette device used. The majority of e-cigarettes purchased today are one of two "types:" customizable tanks or pods. These e-cigarette types differ from each other in critical ways, like nicotine delivery and sensory characteristics, that are likely to impact use by influencing the relative reinforcement value of the product. The present study will be a randomized trial investigating the impact of e-cigarette device type on reinforcement value and use among current smokers. Current smokers (n=100) will be randomly assigned to either a control group that does not receive an e-cigarette or one of two e-cigarette types: a customizable tank, or a pod. The impact of device type on relative reinforcement value will be assessed using a choice task. Participants will also take home their assigned e-cigarette for a three-week sampling period. Primary outcomes include relative reinforcement value (choices to smoke in the lab-based choice task), cigarette smoking behavior (cigarettes smoked per day during sampling), and uptake (e-cigarette puffing episodes per day during sampling).

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Specific Aims

The prevalence of e-cigarettes has risen dramatically in the United States, and the impact of these products on public health remains controversial. Proponents of e-cigarettes argue that because e-cigarettes deliver lower levels of toxicants than conventional cigarettes[1-4], they may offer reduced health risks for current smokers who switch completely[1,4,5]. However, while e-cigarettes appear to offer a path away from smoking for a subset of smokers, a large proportion of those who try e-cigarettes abandon them after a short trial period, or continue to use both products (i.e., dual use)[6-8]. Complete switching from cigarettes to e-cigarettes among those who try them is modest at best. Since the ultimate impact of e-cigarettes is likely dependent on their ability to curb cigarette smoking[9], it is important to understand the device characteristics (in addition to user characteristics: not studied here) that contribute to their uptake. One major and perhaps most visible device factor that determines uptake is the type of e-cigarette itself. The sheer volume of e-cigarette brands makes it impossible to test the impact of each brand (over 400 estimated brands)[10]. However, most e-cigarettes can be categorized into one of four broad types with distinct characteristics: cig-a-likes, tanks, customizable tanks, and pods[11].

There is strong evidence that cig-a-likes deliver less nicotine, are less satisfying, and are less likely to promote switching than other device types[12,13]. Thus, these devices are not included in the proposed project. Tank devices have a nicotine delivery profile differs markedly from traditional cigarettes[14], and thus have also not been included here. The other two types, customizable tanks and pods, corner significant portions of the e-cigarette market and differ from each other in critical ways that would be expected to impact uptake, and thus constitute our primary focus. *Customizable tanks* deliver nicotine in a profile that more closely models the nicotine delivery of traditional cigarettes[14]. These devices offer a high level of customization that allows users to adjust the device until they reach their desired sensory and nicotine delivery settings. However, the customization renders them relatively complicated to learn to use. *Pods* (e.g., JUUL) are the newest type of e-cigarette on the market. Pods utilize nicotine salts, rather than free-base nicotine, which the company claims allows them to deliver high levels of nicotine in a profile that is comparable to traditional cigarettes [15]. They offer no customization, making them easy to use. The combination of high nicotine delivery with increased usability may increase the relative reinforcement value of these products, resulting in greater uptake than other device types. **There is almost no existing research that directly compares these device types against each other[14]. The goal of this application is to provide a preliminary assessment comparing e-cigarette device types (customizable tanks, pods) in a head-to-head design.**

In a between-subjects design, adult daily smokers (n=100) who are interested in trying e-cigarettes will be randomly assigned in 1:2:2 fashion to either a control group that receives no product (n=20), or to receive one of two types of e-cigarettes to sample over a three-week period: a) customizable tank, or b) pod, (n=40/group). The design is naturalistic in that participants receiving an e-cigarette will be told to use the e-cigarette as much or as little as they would like, allowing for assessment of self-determined uptake and reinforcement. Methods include both ecological assessments (electronic daily diaries) and experimental sessions (choice and purchase tasks). Biomarkers (expired carbon monoxide) will corroborate self-reported indices of use.

Primary Specific Aim: to assess the impact of e-cigarette product type (customizable tanks vs. pods) on product satisfaction ratings and relative reinforcement value (choices to smoke vs. use product in choice task, hypothetical purchase task). We hypothesize that pods will produce greater satisfaction ratings and relative reinforcement value than the customizable tanks.

Secondary Aim: to assess the impact of e-cigarette product type on tobacco use patterns including cigarette smoking (cigarettes per day, expired breath carbon monoxide) and e-cigarette uptake (e-cigarette puffing episodes). We hypothesize that pod style e-cigarettes will produce greater reductions in cigarette smoking compared to customizable tanks and greater uptake of e-cigarettes. Secondary analyses will compare the impact of e-cigarette sampling (control vs. all e-cigarette groups) on smoking during the sampling period.

Relevance to Tobacco Regulation: We recognize that e-cigarette device types differ from each other in multiple ways, and it will not be possible to isolate the mechanism by which one type performed better than others (e.g., nicotine delivery, appearance, customization). We view device heterogeneity as a strength since this design mimics the real-world options that smokers face when adopting e-cigarettes but with randomized design to enhance rigor. The goal here is to provide useful information to regulatory agencies and consumers about which types provide the highest reinforcement value and lead to the greatest uptake, *inclusive of the differences between types*. Understanding the impact of device type would provide guidance about which e-cigarette smokers might choose, while at the same time providing key information to the FDA about how to better regulate

e-cigarettes for the improvement of public health. This proposal is in line with funding opportunities from FDA and NIDA.

Significance

A1. Patterns of E-cigarette Use: E-cigarettes have dramatically risen in popularity in recent years[16-18]. Proponents of e-cigarettes argue that because e-cigarettes deliver lower levels of toxicants than conventional cigarettes[1-4], they could offer reduced health risks for current smokers who switch completely[1,4,5]. However, the impact of e-cigarettes on cigarette smoking remains largely unknown[9].

A2. The Impact of Product Type on Reinforcement Value and Use: Smokers have 400+ different e-cigarette brands from which to choose,[10] which vary across many characteristics including appearance, nicotine concentration, device power, flavoring, e-liquid constituents, potential for customization, throat hit, and volume of aerosol production. Full scientific evaluation of these characteristics would be difficult. Instead, we believe it is better and more ecologically valid to test different *types of products*. Here, we focus on two popular device types that collectively comprise about 90% of the e-cigarette market[32] and can deliver nicotine at levels that are comparable to combustible cigarettes[14,33,34]. Customizable tanks use refillable tanks and are activated by pushing a button, but are larger in appearance and offer a high degree of customization to the user (e.g., wattage, resistance, air flow)[11]. Pods, the newest category of devices, often resemble a flash drive in appearance, are activated by drawing on the device rather than pushing a button, are low in wattage, and use a high nicotine concentration e-liquid[11]. JUUL, the most popular pod, has recently surged in popularity[35]. These types of devices have different characteristics that are likely to collectively impact the relative reinforcement value of the product in comparison to a current smoker's usual brand. Relative reinforcement value refers to the degree to which users like/enjoy/want/prefer these alternative e-cigarettes, in comparison to combustible cigarettes. Estimates of relative reinforcement (e.g., purchase tasks, preference tasks) are well-established measures of drug abuse liability and have been utilized for making drug-related policy and regulatory decisions[36-39]. Because the e-cigarette market is changing rapidly, **we know relatively little about the impact of device type on reinforcement value, nor do we have sufficient studies of cross-device comparisons**.

A2a. Nicotine Formulation, Sensory Characteristics, and Customization Potential: Pods deliver nicotine using nicotine salts, rather than free-base nicotine used by customizable tanks. There is no published research directly examining the impact of salts on reinforcement or use, but the makers of JUUL, the most popular pod, claim that using nicotine salts allows for high nicotine delivery with a smooth nicotine hit[15,46].

Several sensory characteristics may be important. First, because pods devices are low powered devices, they produce less visible aerosol than customizable tanks[50,51]. Second, the two device types generate different user topographies. Pod devices are often vaped into the mouth before being inhaled into the lung (i.e., mouth-to-lung), while customizable tanks are inhaled directly to the lungs without first lingering in the mouth (i.e., direct-lung)[52]. Third, "throat hit" is often described as an important sensory characteristic of tobacco use, and the two device types may offer throat hits with different strengths[52,53].

One of the characteristics that distinguishes customizable tanks from pods is that they are, indeed, highly customizable. No published research has directly examined the impact of e-cigarette customization on reinforcement value or use. We know that in general, people are more motivated to engage in an activity when there is choice involved[54], but added customization also introduces more complexity, which could lead to decreased uptake. User satisfaction can also be decreased when there are too many options available[55].

A3. Scientific Premise: The ultimate impact of device type on consumer uptake and downstream changes in cigarette use is likely dependent on the combined impact of all of these characteristics (nicotine delivery, sensory characteristics, customization potential), which together function to change the relative reinforcement value of using e-cigarettes compared to smoking. Despite the importance of device type, there are no published studies which directly compare the type of e-cigarette device on reinforcement value or use. Thus, the goal of the proposed IDEA award project is to provide a preliminary assessment, through a randomized design, of the impact of e-cigarette device type on reinforcement value, uptake, and cigarette smoking behavior. We hypothesize that pod e-cigarette devices, which are sleek in appearance, easy to use, have sufficient nicotine delivery, are used in a mouth-to-lung topography that is similar to cigarette smoking, and have a strong throat hit, are likely to generate the highest level of reinforcement value and uptake.

Reviewers will be quick to note that any comparison of devices will inherently introduce a number of potential confounds. We view this as a strength, not a weakness. We considered an alternative approach that would hold all aspects of a single device constant and isolate specific e-cigarette characteristics. However, research isolating individual characteristics is also quite limited in its implications because devices differ from each other in multiple ways. The ultimate impact of any given e-cigarette on reinforcement value and use will depend on the *combined effect* of all device and e-liquid characteristics. The proposed research takes a complementary approach which is more ecologically representative of the current market: testing differences in e-cigarette characteristics in the same way consumers experience them, as different device types. Thus, this is the most "real world" cross-product test of different e-cigarettes on behavior.

A. Innovation

The proposed study is highly innovative, timely, and important given the current landscape. First, this will be the first trial to compare customizable tanks and pods using an experimental design. Large, longitudinal trials, like the Population Assessment of Tobacco and Health[62], provide information about the relative popularity of these device types. However, these datasets are limited because smokers are not randomized to a specific device, and thus, cannot provide critical information about the causal impact of device type on reinforcement value and use. The randomized design utilized in this study is one of its primary strengths. Second, this project is innovative for its use of the JUUL product specifically. In 2016, JUUL (a popular pod brand) comprised 2% of sales in retail outlets[35], but that number climbed to 29% in December of 2017[35] and 76% in November of 2018 [63]. Because of how rapid the rise in popularity has been, there is almost no existing research which investigates its impact. To the best of our knowledge, there are no published experimental studies investigating JUUL and no published reports focusing on JUUL use among current smokers.

C. Approach

C1. Design and Procedures: Consented participants will complete screening measures to determine eligibility. Eligible adult smokers will be randomly assigned in a 1:2:2 between-subjects design to either not receive an e-cigarette (control group, n=20) or receive one of two e-cigarette types: a customizable tank, or pods (n=40/each). Participants will sample their assigned e-cigarette, complete questionnaires, and then complete the choice task (described below). Participants will be provided with an e-cigarette device and e-liquid to sample over a three-week period (Figure 1). Across the study, participants will complete daily electronic diaries that assess their daily use of cigarettes and e-cigarettes. Participants will also complete weekly phone calls where they will complete assessments regarding tobacco use, craving, dependence, and product perceptions. At the end of the sampling period, participants will return to the lab to complete a series of questionnaires. complete the sampling and choice tasks again, and return the device.

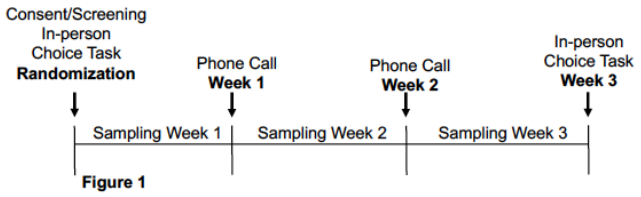


Figure 1

C2. Participants: Daily cigarette smokers (n=100) will be recruited from the community. In/exclusion criteria are designed to enroll smokers who have limited experience with e-cigarettes. Inclusion criteria include adults who a) 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) willing to use an e-cigarette as part of the trial, d) have a smartphone that can receive text messages and has access to the internet or have an e-mail account they check daily (necessary for daily diary completion) and e) be at least 21 years of age. Exclusion criteria include a) purchasing an e-cigarette within the last six months, b) weekly use of e-cigarettes over the last six months, c) any e-cigarette use in the past 30 days, d) use of tobacco products other than cigarettes on ten or more days in the past 30 days, e) current use of cessation medications, f) pregnant, trying to become pregnant, or breastfeeding, g) recent history of cardiovascular distress in the last three months, h) history of a seizure disorder, or i)household member currently enrolled. We will stratify group assignment based on age (21-30 vs. 31+) and motivation to quit (0-6 vs 7-10) to prevent these variables from being confounded with group.

C3. E-cigarettes and e-liquids: The best exemplars will be chosen from each of two device type categories based on market share data. Currently these include the Mirage DNA 75C e-cigarette (customizable tank style), and a JUUL e-cigarette and pre-filled pods (pod).

Participants will be provided with one device, one charger, and a choice of e-liquid flavors. Participants will be able to choose up to two flavors (to allow for switching of flavors during sampling) from a menu of four flavors. For the customizable tank/Mirage device, e-liquid is sold separately which is the case with all customizable tanks. E-liquid will be available in a wide array of flavors, and will be provided in 12 mg/ml nicotine concentration. For the pod/JUUL devices, we will provide each participant with one pre-filled e-liquid pod for each day of sampling. These pods provide enough nicotine to compare to one pack of cigarettes, and thus one pod per day should be sufficient. E-liquid will be 5% nicotine, which JUUL states is the most popular nicotine concentration they sell. All participants will receive instructions on how to operate their device, fill it with e-liquid or replace the pods, and be given a lab phone number to call with questions. Participants assigned to the customizable tank device will be shown how to adjust their customization settings.

C4. Compensation Participants will receive $50 for the screening/randomization if they are eligible and $15 if they are not. Participants will receive $50 for the Week 3 visit, $20 each for the Week 1 and Week 2 phone calls, and a $50 completion bonus if they complete all assessments. Participants will also receive up to $25/week for completing daily diaries (up to $75). Thus, participants who attend all visits and complete all diary entries could earn $265.

C5. Measures

C5a. 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.

C5a. Measures of Subjective Effects: Subjective effects will be assessed using a modified version of the Cigarette Evaluation Questionnaire (mCEQ)[66], which assesses product satisfaction, psychological reward, craving reduction, enjoyment of sensations in the respiratory tract, and aversion. First, participants will sample their usual brand cigarette to standardize time since last cigarette. Participants will then sample their assigned e-cigarette and e-liquid. Immediately after sampling, participants will complete the mCEQ.

C5b. Measures of Relative Reinforcement: Relative reinforcement will be assessed using a lab-based choice task, a well-validated measure of reinforcement value[67]. After participants sample their assigned product, they will complete choice task in which over a period of 30-minutes and 10 trials, participants choose between taking two puffs of the e-cigarette, two puffs of their usual (own) brand cigarette, or abstaining from both. Participants in the control group will choose between their usual brand cigarette and abstaining. In this case, the task will measure the impact of device type on changes in the relative reinforcement value of smoking compared to using the e-cigarette. The primary outcome is the number of choices to smoke. A secondary measure of reinforcement value will be purchase tasks—hypothetical tasks in which participants estimate the intensity with which they would use cigarettes and e-cigarettes at a variety of prices[68,69]. The purchase tasks can be used to calculate several demand parameters, which are estimates of reinforcement value[36]. Additional dependence measures will be included [707172]. Dr. Smith is utilizing these measures in recently completed and upcoming projects.

C5c. Measures of Tobacco Use and Biomarkers: Daily cigarette use will be captured using an electronic daily diary (<2 min/day) in which participants report the number of e-cigarette puffing episodes per day and the number of cigarettes they smoked. This electronic daily diary was used in Dr. Smith's recently completed trial with compliance > 90%. We will collect expired breath carbon monoxide at Randomization and the Week 3 visit, which provides an objective measure of recent smoke exposure but is unaffected by e-cigarette aerosol.

C5d. Other Self-Report Questionnaires: We will also use questionnaires to assess demographics, tobacco use history, expectancies, perceived health risks, and adverse events over time.

C6. Statistical Analysis, Power, and Predicted Outcomes

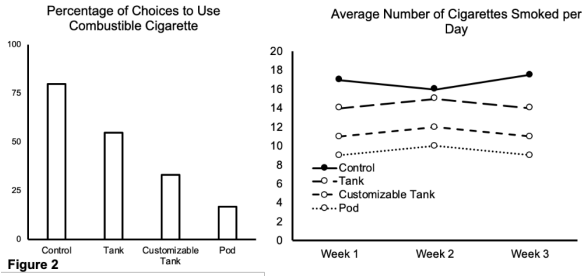


Figure 2

C6a. Statistical Analysis: We focus on changes in reinforcement value of cigarettes because the public health impact of e-cigarettes will be driven by changes in the use of cigarettes, rather than any direct effects of e-cigarettes. Our primary outcome is the percentage of choices for each participant to smoke the conventional cigarette during the choice task at Week 3 (ranging from 0 to 100%). A one-way ANOVA model will be used to compare the e-cigarette groups, while excluding the control group, to examine the effect of e-cigarette type. If there is no significant difference between e-cigarette types, e-cigarette participants will be combined and compared to the control group via a t-test to examine the effect of e-cigarette sampling. Other outcomes will be analyzed using general linear mixed models (GLMMs) controlling for baseline values and repeated measurements per participant will be used to examine group, time, and group by time interactions. Our secondary aim focuses on the average number of cigarettes smoked per day during Week 3 while also examining average e-cigarette puffing episodes, expired carbon monoxide. These outcomes will be examined in a similar manner via GLMMs. We will also conduct exploratory analyses to determine whether the effect of e-cigarette type or e-cigarette sampling depended on individual characteristics such as age, gender, race, and motivation to quit. Given the innovative and exploratory nature of this trial, there are no existing datasets that directly apply for the purposes of conducting a power calculation. However, a sample size of 30 per e-cigarette group will provide 80% power to detect moderate between-group differences in a one-way ANOVA comparing the primary outcome with a two-sided alpha=0.05.

C7c. Predicted Outcomes: We hypothesize that the pod e-cigarette will result in further reductions in choices to smoke during the choice task and in cigarette smoking (Figure 2).

C8. Future Directions: The goal of the proposed application is to gain preliminary data on the impact of e-cigarette type. An R01 grant application will follow the proposed project and will include a longer sampling period, longer follow up period, a more thorough investigation of the health effects of e-cigarette types, and a full investigation of any critical moderators (e.g., age).

C9. Timeline: The proposed study will take one year. The first three months will be devoted to study start up, measurement finalization, IRB approval, obtaining product, etc. Our prior studies will steer this process efficiently. We will recruit approximately eight participants/month for 9 months, until 100 participants have been randomized. An R01 grant application will be submitted in the Fall of 2020.

Protection of Human Subjects

1. Risks to Human Subjects

1.1 Human Subjects Involvement, Characteristics, and Design:

Current smokers will be randomly assigned in a 1:2:2 between-subjects design to either not receive an e-cigarette (control group, n=20) or to receive one of two e-cigarette types: a customizable tank, or pods (n=40/each). All participants will receive an e-cigarette and e-liquid to sample over a three-week period.

1.2 Study Procedures, Materials, and Potential Risks:

Study Procedures:

Participants will be screened over the phone to determine initial eligibility. Alternatively, 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). 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. We will provide transportation via a taxi cab company (Yellow Cab) for participants who are eligible, but do not have reliable transportation to in-person visits. We will pay the cab company directly, the participant will not need to contribute. 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 complete additional baseline questionnaires including measures of nicotine dependence. Participants will be randomized 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 three-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 complete weekly phone calls after one and two weeks of sampling and will return to the lab for an in-person visit after three weeks of sampling. At each visit or phone call, we will assess tobacco use during the prior week, adverse events will be assessed, and participants will complete questionnaires about their assigned e-cigarette and e-liquid. At each in-person visit, participants will provide an expired breath carbon monoxide sample. At the fourth and final weekly visit, participants will complete the sampling and preference assessment again, and return any unused study product.

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 visit 2, we will complete any questionnaires remotely that we can be completed 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.

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.

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.

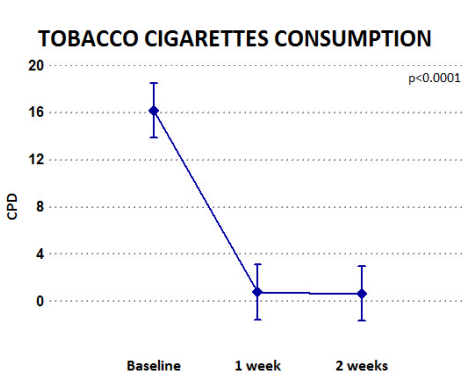
As for adverse events, the majority of e-cigarette studies are based within on-line surveys. We report here on three moderate to large such surveys. In the first (98), three side effects were reported by >20% of respondents: headaches (21%), cough (27%), and increased phlegm (25%). In the second (99), 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.

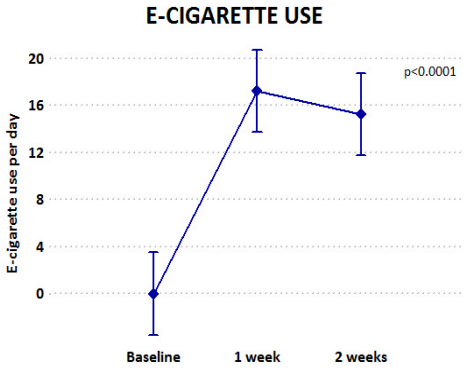
There have been a small number of reports to the FDA of people using e-cigarettes and experiencing seizures, with most reports involving youth or young adult users. This is rare and will be monitored. We have added an exclusionary criteria for history of seizure disorder.

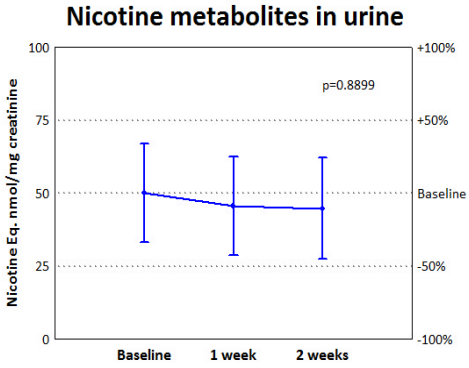
There have been a number of reports of respiratory illness, and even some deaths from that respiratory illness, among individuals using e-devices. No specific substance or product has been linked to these cases. Many of but not all of the cases involved users vaping THC, the active ingredient in marijuana. 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. Once initial eligibility 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). During COVID-19 restrictions, all consenting will be done remotely. 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/HIPAA 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. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Each signed consent/HIPAA can be downloaded from REDCap as a PDF. 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.

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 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.

Data and Safety Monitoring Plan

All participants entering into the study will be closely supervised by the research staff during the study 3-week study period. Providing e-cigarettes to smokers over a short sampling period incurs minimal risk, with no invasive procedures. Cessation resources will be provided to all participants upon end of study procedures. The PI will directly monitor all aspects of study procedures, including recruitment, assessment, and test sessions.