**SPECIFIC AIMS**

E-cigarette use is common in young adults, a portion of who have no history of regular combustible tobacco use. This group may face harms from vaping, including nicotine dependence and increased risk of combustible tobacco use.\(^1\)\(^-\)\(^8\) In contrast, regular smokers, who vary in age, may garner health benefits by switching to e-cigarettes.\(^7\) Thus, regulation of e-cigarettes in a manner that protects “the population as a whole,” a requirement of the Tobacco Control Act, poses a challenge in balancing potential harms and risks of e-cigarettes.\(^8\)

This study aims to provide the FDA with evidence necessary to inform regulatory restrictions of dimensions of e-cigarette product diversity that affect use of e-cigarettes, including those that might put young adults at risk of using e-cigarettes yet do not deter smokers from adopting and potentially transitioning to e-cigarettes. We hypothesize that several dimensions of e-cigarettes may affect use of e-cigarettes overall, and differentially across populations varying in age and smoking status. Example product dimensions include - Flavors: Young adult vapers may prefer e-liquids with sweet flavorings due to neurodevelopmental taste sensitivity preferences,\(^9\) and menthol flavors that mask the bitterness of nicotine.\(^10,11\) Sweet flavors may be less important for middle-age/older adult smokers who may be more accustomed to and prefer traditional tobacco flavorings.\(^12\) Nicotine formulation: Increased e-cigarette nicotine concentrations in free-base have been shown to modulate the product appeal and sensory effects (i.e., throat hit / irritation to airways) of e-cigarettes\(^13\) and may affect smoking and vaping.\(^14\) E-liquids that produce a weak irritation\(^15\) may appeal to young adults, while smokers may prefer vapor that more closely resembles, and is thus a better substitute for, cigarette smoke (stronger throat hit).\(^16\)\(^-\)\(^18\) Recently, e-cigarette devices that utilize protonated (vs. free-base) nicotine formulations (e.g., Juul) have become popular among youth, but their effects on appeal, sensory effects, and abuse liability are unknown. Packaging/marketing: packaging is a key conduit for marketing approaches that target youth, including labels with youth-oriented product themes (e.g., ‘Gummy bears’), which may not appeal to middle-age/older adults.

We will assess the effect of variation in each e-cigarette product dimension on 3 proximal outcomes of relevance to FDA regulation: (1) Product appeal; (2) Abuse liability; (3) Ability to resist the temptation to smoke cigarettes\(^19,20\) in two human laboratory experimental studies. Our Specific Aims are:

**Aim 1. Evaluate the association of each product dimension with subjective ratings of appeal among e-cigarette users and smokers with an interest in, but no significant experience with, e-cigarettes, varying in age.** Participants will self-administer e-cigarette products systematically varied according to flavor (e.g., sweet vs. menthol vs. tobacco), nicotine formulation (e.g., salt vs. free-base), and will be presented with varying packaging (e-liquid plain flavor name [e.g., “Peach”] vs. youth-oriented flavor name [e.g., “Peach Gummy Bears”]) for each administration. The use of an efficient within-subject factorial design will minimize the sample size needed to assess the main effect of each product dimension. Participants will provide subjective ratings of each product (e.g., desire to use again), which will be utilized to assess the relative appeal of each dimension, with the primary goal of studying product dimension effects in the overall population of tobacco-product users and the secondary goal of studying differences in product characteristic effects on appeal across non-smoking vapers and smokers.

**Aim 2. Evaluate the association of each product dimension with abuse liability among e-cigarette users and smokers with an interest in, but no significant experience with, e-cigarettes, varying in age, and ability to resist smoking in current smokers.** Studies using an efficient factorial design will be utilized wherein each participant will be administered a product with one set of conditions (e.g., sweet flavor, nicotine free-base formulation, youth-oriented flavor name). After product administration, participants will complete either: (a) an abuse liability task measure of the reward value of the previously sampled product or (b) a similar task directed towards measuring the impact of e-cigarette product administration on ability to resist smoking their preferred brand of cigarettes (current smokers only). A factorial design will be used to evaluate the main effect of each primary product domain, by collapsing data across the other conditions; thus, each analysis provides an opportunity to assess product dimensions with the same sample, maximizing the efficiency of the study, with the primary goal of studying product dimension effects in the overall population of tobacco product users and the secondary goal of studying differences in product characteristic effects across non-smoking vapers and smokers.

To compare effects across smoking statuses, formal group (e.g., vaping non-smokers vs. smokers) × product dimension (e.g., flavor, nicotine, or packaging) interaction tests will be used to evaluate hypotheses regarding divergent effects, resulting in: (Aim 1) greater product appeal in young adult vapers relative to smokers, and (Aim 2) greater abuse liability in never-smoking vapers relative to efficacy in increasing ability to resist smoking in smokers.
**RESEARCH STRATEGY**

**A. SIGNIFICANCE**

A.1. Health Effects of e-Cigarettes in Young Adult Vapers vs. Adult smokers.

**A.1.1. Reasons for e-cigarette vaping in young adults.** Vaping in young populations is predominantly done for recreational purposes; the most commonly reported reasons for use in this group include curiosity, enjoyment of flavors, enthusiasm for being part of vaping culture, blowing large vapor clouds, and wanting to fit in with peers who vape.\(^{21,22}\) 40% of 18-24 year old current e-cigarette users in the U.S. in 2014 reported no history of regular combustible cigarette smoking (≤100 cigarettes throughout lifetime),\(^{23}\) and few young adults report that a primary reason of e-cigarette use is to replace combustible cigarette smoking.\(^{21,22}\)

**A.1.2. Potential Adverse Health Outcomes Associated with Vaping in Young Adult Vapers.** Experts have cited three key concerns about e-cigarette use in youth and young adults: (1) **Exposure to potential toxins in e-cigarette aerosol.** Research suggests that e-cigarette aerosol includes toxic compounds and produces biological changes and symptoms implicated in cardiovascular disease, respiratory illness, cancer, and other adverse health conditions.\(^{24-26}\) The U.S. Surgeon General’s Report on e-cigarettes in Youth and Young Adults concluded that nicotine exposure causes neurobehavioral consequences due to adverse effects of nicotine on the developing youth brain.\(^{27}\) While the e-cigarette toxicity literature is nascent and the magnitude and clinical significance of these exposures are not yet clear, precaution regarding e-cigarette exposure in young populations remains a salient concern in the public health community, relevant to the regulation of e-cigarettes.\(^{28}\) (2) **Risk of e-cigarette nicotine dependence.** While the dose of nicotine reaching the bloodstream varies across different e-cigarette products, certain products (e.g., those with high wattage and e-liquid nicotine concentrations) can deliver nicotine in doses that equal or exceed those delivered by standard cigarettes.\(^{29}\) Observational data indicate that individuals who vape but do not use other tobacco products exhibit symptoms of nicotine dependence (a recognized psychiatric syndrome associated with clinically-significant distress) due to their e-cigarette exposure.\(^{30}\) While preliminary evidence suggests that the clinical severity of e-cigarette dependence is less severe than combustible cigarette dependence,\(^{30}\) concerns remain that e-cigarette exposure could lead to a novel form of nicotine dependence and contribute to the tobacco product health burden in young adults.\(^{31}\) (3) **Risk of uptake of other tobacco products and health-damaging substances.** Prior research from USC and others has shown that exposure to e-cigarettes in youth and young adults is prospectively associated with future risk of initiation, use, and progression to cigarettes, other forms of combustible tobacco, and other health-damaging substances (e.g., cannabis).\(^{1-4,32,33}\)

**A.1.3. Transitioning from Combustible Cigarettes to e-Cigarettes among Adult Smokers.** The most common reason that middle-age/older adult smokers (aged ≥30 years; daily smokers of at least 2 years) cite for interest in and use of e-cigarettes is to quit smoking.\(^{34}\) E-cigarettes occupy a unique niche among the various tobacco and nicotine products currently available. E-cigarettes do not deliver combustible tobacco smoke; as such, the aerosol lacks the overall toxicity of tobacco smoke and some of the byproducts of combustion that are known causes of smoking-related diseases. E-cigarettes also differ from oral non-combustible tobacco products (e.g., nicotine gels, dissolvables, snus, smokeless tobacco) and standard nicotine replacement therapy products (NRTs: transdermal patch, gum, lozenge) in delivering pulmonary nicotine more rapidly in the form of acute ‘boluses’ at rates and dosages similar to those found in cigarettes.\(^{35}\) Nicotine in ‘bolus’ form (vs. via gradual delivery in other products) produces stronger pharmacological effects on nicotine withdrawal and therefore may be better positioned to adequately substitute for cigarettes, satiate smoking urges, and enhance ability to resist the temptation to smoke.\(^{36}\) E-cigarettes also provide sensorimotor stimulation that mirrors cigarette smoking (e.g., taste of aerosol, stimulation of the airways and throat hit, inhalation, exhalation, hand-to-mouth movements, and appearance of smoke-like aerosol), which impacts smoking behaviors.\(^{37}\)

While evidence on the long-term safety and the efficacy of e-cigarettes to facilitate smoking cessation is not yet available, results from observational studies have been mixed: positive, negative, and null associations have each been reported for e-cigarette use and smoking cessation.\(^{38}\) Efforts to identify possible moderators of observational associations suggest some product characteristics under which e-cigarette use may improve cessation outcomes (e.g., daily use of high-wattage tank style devices), but the evidence remains highly preliminary.\(^{39,40}\) Initial results from phase I-II clinical trials and laboratory studies are somewhat promising and suggest that administration of e-cigarettes with nicotine reduces nicotine withdrawal symptoms, increases odds of cessation, and reduces exposure to toxic compounds in cigarette smoke by reducing smoking behavior.\(^{41,42}\)

**A.1.4. Hypothesized Benefits of Transition for Smokers.** While the evidence base remains limited, there are two potential health benefits of e-cigarette use in middle-age/older adults with histories of regular smoking: (1) **Potential for complete cessation of all tobacco products.** Like therapeutic NRT regimens, smokers who adopt e-
cigarettes may transition to a temporary state of exclusive e-cigarette use without smoking, followed by subsequent stoppage of all tobacco products. While robust data on the probability of complete cessation of tobacco products via e-cigarettes is still lacking, those who achieve this outcome are likely to experience substantial health benefits that may be comparable to cessation achieved through other means. (2) Opportunity for transition to exclusive e-cigarette use. Recent studies of smokers who do not wish to quit have shown that adoption of e-cigarettes can substantially reduce frequency of cigarettes consumed (e.g., reduction in cigarettes per day, moving from daily to non-daily smoker), or lead to cessation. While the relative health benefit of long-term e-cigarette vs. cigarette use is not known in the absence of quitting via other traditional methods, this outcome may be associated with meaningful health benefits.

A.1.5. Enthusiasm Regarding the Potential Reach of e-Cigarettes for the Adult Smoker. Expert commentary and results from impact analysis studies on the public health benefit of e-cigarettes cite the impact model of efficacy × reach. That is, while first line cessation treatments like counseling and medication are efficacious, very few smokers adopt such treatments. In contrast, even if e-cigarettes are modestly efficacious (including less effective than certain medications and counseling strategies), the potential that e-cigarettes may be more appealing, easier to access, and less burdensome than front-line treatments may facilitate their wide adoption, and hence, larger population-level impact relative to other cessation strategies. A smoking cessation clinical trial in New Zealand comparing nicotine e-cigarettes vs. patch NRT found no significant differences in smoking cessation outcomes, however adherence to product use was much higher in participants in the e-cigarette condition than the NRT condition. These results suggest that e-cigarettes may be more appealing than NRTs and as a result, may have greater real-world effectiveness than NRTs.

A.2. The Prevalence of e-Cigarette Use by Age in the U.S. Population is Concerning. The prevalence of current e-cigarette use in the 2013-2014 Population Assessment of Tobacco and Health (PATH) survey decreases by age among adults: 18-24 years (8.9%), 25-34 years (8.3%), 35-44 years (6.3%), 45-55 years (5.1%), 55-64 years (4.1%), 65+ years (1.5%). In middle-age/older adults, e-cigarette products appear to garner some interest, but very few adults who try e-cigarettes maintain use. Estimates from PATH show that while 15.6% of adults aged ≥25 years had tried e-cigarettes, only 1.2% adopted e-cigarettes for regular use. The low levels of adoption of e-cigarettes after initial trial among middle-age/older adult smokers pose a barrier to leveraging any putative positive impact of e-cigarettes on the tobacco burden. It is possible that the majority of e-cigarette products available in the current regulatory environment appeal to youth and young adults, but not to middle-age/older adult smokers. Thus, if such youth-oriented products were no longer available, the marketplace would be less crowded by products with little potential to facilitate transitions away from smoking. The remaining e-cigarette products, when purchased, may be more attractive to middle-age/adult smokers and engender regular use to maximize any potential for complete transition to e-cigarettes without smoking.

A.3. Regulation of e-Cigarettes that Protects Young Adult non-smokers, without Obstructing Any Potential for Transition in Smokers. Commentaries from the public health community discussing the issue of e-cigarette-related risks in young populations and transition opportunities in middle-age/older adult smokers have typically approached recommendations for e-cigarette regulation from a unidimensional perspective, ranging from highly restrictive to highly permissive, with those concerned about youth arguing for restriction and those enthusiastic about transition in adult smokers arguing for permissive policies. Instead of merely applying a unidimensional perspective, we propose that regulation can instead be more precise. Given the tool kit of options within the purview of federal regulation, we propose that regulatory policies can be more precise and prevent use of tobacco products (including e-cigarettes) among young non-smokers, without discouraging middle-age/older adult smokers from adopting e-cigarettes to replace combustible tobacco.

Section 907 of the Federal Food, Drug, and Cosmetic Act on Tobacco Product Standards requires that the FDA review and approve of all new tobacco products before they can be introduced to the market. The FDA can, if deemed appropriate for the protection of public health, prohibit new products from being marketed, sold and distributed. The FDA may also require changes in existing tobacco products to meet new product standards to be based on available evidence with respect to the risks and benefits to the population as a whole: “including users and non-users of tobacco products, taking into account the increased or decreased likelihood that existing users of tobacco products will stop, and that nonusers will start” due to the policy change. The product dimensions within the purview of FDA product standards, include, but are not limited to, product constituents, components, and packaging labels. In addition, regulatory marketing requirements have long been applied to cigarettes to prevent appeal of tobacco products to youth. Given the FDA’s ‘population as a whole’ standard, evidence that meets this definition would be policies that restrict the availability of e-cigarette products that: (1) Attract adoption and progression to regular use in young populations; (2) Have minimal attraction to regular
smokers who wish to, or have already, switched to using e-cigarettes only.

A.4. Research Questions that will be Addressed in the Proposed Project. The proposed research aims to identify whether variation in several domains of e-cigarette product diversity affect outcomes relevant to use overall and disproportionately: (1) Increases e-cigarette appeal in young adult e-cigarette users relative to middle-age/older adult smokers; (2) Increases abuse liability (i.e., potential dependence) in young adult e-cigarette users; (3) Relatively improves the ability to resist smoking in middle-age/older adult smokers. These domains were chosen for the following reasons:

A.4.1. Flavoring. Flavoring additives, including sweeteners and ingredients to generate gustatory responses that parallel tastes found in common foods, drinks, and desserts, are extremely common in e-liquids and highly numerous in the marketplace. In the 2009 Tobacco Control Act there is a precedent set for combustible cigarettes that bans characterizing flavors (other than menthol) of the tobacco product or smoke. In the 2016 Deeming Rule, which did not restrict flavoring in e-cigarettes, the text notes: “FDA understands that the appeal of flavors and use of flavored tobacco products have an important role in the initiation and continued use of tobacco products, [and] have determined that exercising enforcement discretion indefinitely could put youth and young adults at risk for tobacco-related death and disease. However, we recognize that the availability of alternatives to traditional tobacco flavors in some products (e.g., ENDS) may potentially help some adult users who are attempting to transition away from combusted products.” The evidence available at the time of the rule was insufficient for forecasting whether product standards related to flavoring met the “population as a whole” standard. By providing evidence as to whether certain flavors disproportionately enhance appeal and abuse liability among young adult e-cigarette users, but do not appeal to or aid the ability to resist smoking in middle-age/older adults, this research could inform whether flavoring restrictions are worth considering in future e-cigarette product standards for the protection of the public as a whole.

A.4.2. Nicotine. Nicotine is the primary psychoactive constituent that maintains dependence to tobacco products. The adolescent brain is particularly vulnerable to the addictive and harmful effects of nicotine, but nicotine alone is considered minimally harmful to adults. Controlled laboratory evidence demonstrates that higher e-cigarette nicotine concentrations affect product appeal and sensory effects (i.e., throat hit) of e-cigarettes. Epidemiological evidence suggest that adolescent vapers who use e-cigarettes with greater nicotine concentrations are more likely to exhibit increased past 30-day frequency and daily intensity of smoking and vaping. Hence, nicotine could affect abuse liability among young adult vapers as well as the ability of e-cigarettes to aid adult smokers in tobacco harm reduction (i.e., smoking reduction and cessation). Recently, e-cigarette devices that utilize protonated (vs. free-base) nicotine formulations (e.g., Juul, Suorin) have become popular among youth. However, it is unknown whether the subjective effects, abuse liability and withdrawal-suppressive effects of e-cigarette devices utilizing protonated (vs. free-base) nicotine differ.

A.4.3. Packaging. In the current e-cigarette marketplace, there is a wide variety of marketing themes and images on the packaging of e-liquids, including the labels on the bottles that are linked with a specific flavor name to support a marketing theme message (e.g., conferring themes related to candy or mythological creatures). Such labels are a key point of marketing in all venues, including on social media, in vape shops, or in the social or physical environment. The Tobacco Control Act places specific restrictions on marketing tobacco products to children and gives the FDA authority to take further action in the future to protect public health. According to the 2016 Deeming Rule, there are not yet specific restrictions against marketing youth-oriented themes on e-cigarette product packaging or other e-cigarette marketing and advertising venues. In the 1998 Master Settlement Agreement (MSA) between the major tobacco companies, 46 U.S. states, the District of Columbia, and 5 U.S. territories, marketing restrictions were enacted to prevent direct and indirect targeting of youth. The MSA included a ban on the use of cartoon characters in tobacco marketing, which set a precedent that could be applied in new fixed marketing standards addressing e-cigarettes. Given the wide variety of themes that may differentially appeal across populations, another potential FDA marketing requirement may be limitations on names of products outside a standardized set of flavors (e.g., peach, strawberry, coffee) that would disallow any youth-oriented theme. Further evidence of whether youth-oriented flavor names (e.g., ‘peach gummy bear’) vs. standard flavor names differentially impact appeal across the two groups, without affecting the product’s effect on ability to resist smoking in middle-age/older adult smokers, would clarify the impact of marketing requirements on the overall population.

A.5. Utility of Human Laboratory Paradigms for Tobacco Regulatory Science. The 2010 Conference on the Abuse Liability and Appeal of Tobacco Products concluded that both appeal and abuse liability assessments are recommended to identify and quantify factors that increase product use and addictiveness, regardless of whether
those factors are pharmacological, based on product marketing, product flavoring, or other factors to inform FDA regulation.62 Appeal and abuse liability assessment both involve examining the behavioral effects of experimentally-manipulated product exposure within the controlled confines of the laboratory. Certain forms of product variation, such as constituents in e-liquid (flavorings, nicotine), can be manipulated under double blind conditions, in which the experimenter and participant are unaware of the condition. As such, these approaches permit inferences regarding the causal effects of a particular product characteristic independent of other characteristics, which is critical for informing precise regulatory targets. Appeal assessment examines the impact of product exposure on subjective mood states and reinforcement value. Distinct from appeal, abuse liability is of greater specificity for distinguishing the likelihood that a product will produce persistent use over long periods and dependence. While abuse liability of tobacco products is believed to be driven by pharmacological factors, it may also be influenced by ingredients and design features that facilitate the inhalation and absorption of nicotine into the lungs by reducing harshness and bitterness of the aerosols, such as by sweet or soothing constituents.63 Furthermore, the reward-enhancing pharmacological effects of nicotine, when combined with other pleasant stimuli (e.g., mood states, stimulation of the airways), may also promote synergistic interactions between nicotine and other stimuli in increasing abuse liability.64,65 We will also test the effects of e-cigarette product exposure on a human laboratory analogue measure of the ability to resist smoking, which is used to evaluate whether products or other interventions increase the ability to resist the temptation to smoke and choose an alternative reward vs. the tobacco product.66

B. INNOVATION

To date, most human laboratory research on e-cigarettes has explored clinical pharmacology, with a primary focus on product dimensions that impact nicotine delivery. Here, we establish new dimensions of breadth of tobacco regulatory science based in human laboratory studies. This is achieved by engendering the study of non-pharmacological determinants and effects of e-cigarette exposure, including novel marketing exposure manipulations with a focus on cross-population differences. This paradigm reflects a novel synthesis of consumer behavior research on appeal and behavioral pharmacological research on abuse liability. As such, the study provides a template for future scientific applications to: (1) Non-combustible products such as heat not burn tobacco or snus, that could also have divergent effects across populations of interest; and (2) evaluating how product characteristics and marketing strategies have distinct behavioral effects across subpopulations who differ in vulnerability to the adverse health effects of tobacco product use (ethnic minorities, individuals with low SES, people with HIV and other chronic disease comorbidities, people with mental health problems, etc.).

C. APPROACH

C.1. Expertise of the research team. This study will be led by PI Leventhal, an addiction psychologist who directs the USC Health, Emotion, & Addiction Laboratory (HEAL). Since 2010, HEAL has recruited and retained more than 1,200 smokers and 200 e-cigarette users for laboratory studies involving cigarette and e-cigarette challenge paradigms. Leventhal’s expertise in tobacco withdrawal and nicotine psychopharmacology (DA026831, DA034768, ACS: RSG-13-163-01)67,68 is complemented by three Co-I faculty members of USC-HEAL. Pang is a neuroscientist with expertise in sex differences in nicotine dependence (DA040043).69 Kirkpatrick is a behavioral pharmacologist and abuse liability expert (TRDRP: IP-394035)70,71 who has experience applying multi-level models and other requisite analyses for complex experimental designs and will oversee the analysis for this project. Barrington-Trimis is an epidemiologist with expertise in e-cigarette laboratory administration research and product characteristics (HD084812).4,28,72,73 Dr. Michael Levine, assistant professor of emergency medicine, has served as the study physician for several USC-HEAL laboratory experiments.

C.2. Overview of Project. After a pilot to establish product parameters to be used for all aims (see below), we will conduct a series of factorial-design experiments to address study aims. Factorial designs can be used to efficiently evaluate multiple main effects in a single study utilizing a smaller sample than if such effects were evaluated in separate studies. Factorial designs will be used in both aims that tests the main effects of flavor conditions (various sweet, menthol, mint, an tobacco), nicotine (free-base vs. salt) packaging (regular vs. youth-oriented flavor name), and the other secondary product characteristics based on constituent analysis noted above using an appeal testing paradigm. Aim 1 uses within-subject factorial experiments testing subjective appeal outcomes. In Aim 2, we will conduct a series of experiments using between-subject factorial designs to test the main effects of product characteristic variation on choice to use (vs. earn money): (1) the previously-exposed e-cigarette product (an abuse liability test only); or (2) their own brand cigarettes (test of ability to resist smoking in adult current smokers).
C.3. Pilot Studies. Vapers (N=20) meeting the eligibility criteria in C.4 will attend three experimental sessions in which they will self-administer 3 different e-liquids varying by nicotine formulation (no nicotine, free-base nicotine and nicotine salt) using an experimenter-provided e-cigarette device. Eligible smokers (N=20) will also attend four experimental sessions in which they will use e-liquids with varying nicotine (no nicotine, free base nicotine and nicotine salt) as well as one session in which they will smoke their own preferred brand cigarette. Participants will be asked to include their social media contact information. This information will only be used to contact participants if they change their email address and/or phone number. We will not use this information to follow participants or collect information about them. During each session, participants will complete a pre-administration assessment, self-administer a study-provided e-cigarette (or participant’s own e-cigarette [for those who vape] or own cigarette [for those who smoke]) using a standardized procedure known to produce nicotine plasma levels similar to those produced by smoking a cigarette ([6.4].), and then begin either the behavioral vaping or smoking task (smokers only) (described in C.6.10 and C.6.11). Participants will not be told which condition they received until the end of the study. The rationale for using deception is to allow for the collection of participant’s real, unbiased opinions about each e-liquid. If we were to disclose the levels of nicotine before self-administrations, participants may have expectations about their experiences based on these levels. Vaping and smoking portions of the sessions may be recorded using digital video, for subsequent analysis of smoking and vaping behavior. Video recordings will be identified with only the participant’s number. Original recordings will be stored on our secure server with other electronic data. After analysis is complete, original recordings will be disposed of confidentially. We will obtain an intravenous blood sample from a certified phlebotomist or other licensed health professional capable of intravenous blood draw (e.g., nurse, physician) prior to the e-cigarette administration and approximately 5 minutes following administration (see C.5.11). Each session will occur after overnight tobacco product deprivation and will follow procedures described below (C.5.3). The purpose of the pilot is to ensure feasibility and acceptability of study procedures and products and ensure they result in intended nicotine delivery and characteristic subjective and behavioral effects of nicotine administration. For completing the pilot study participants will be remunerated $300. After completing the study, participants will be told that they self-administered e-liquids with three different concentrations of nicotine. The participant will be told the specific order of the e-liquids that they received at each applicable experimental session.

C.4. Participant Eligibility Criteria for All Studies. These criteria have been used previously and have yielded a high volume of participation and eligibility rates. Inclusion criteria requires past 30-day nicotine/tobacco product use either in the form of e-cigarette use (e-cigarette use ≥3 day/week over the past 30 days; lifetime vaping duration ≥2 months; used nicotine-containing e-cigarettes) or combustible cigarette use (cigarette use ≥3 day/week for ≥2 years; interest in trying e-cigarettes if not also using e-cigarettes). Current smokers that also use e-cigarettes are eligible. Exclusion criteria are: (a) impending plan to quit using nicotine/tobacco products, (b) currently or planning to become pregnant/breastfeeding, (c) current daily use of tobacco products other than combustible cigarettes or e-cigarettes.

C.5. Aim 1 Product Appeal Testing

C.5.1. Design. Participants (N=400) will attend 1 laboratory session in which they will self-administer e-cigarette products varied according to the dimensions described in Section A.

C.5.2. Participants, Recruitment, and Compensation. We will recruit our sample from a combination of resources, including online advertisements, and USC-HEAL databases of past participants. After a brief phone eligibility screen, participants will attend a three-hour in-person experimental session at our facility at the USC Health Sciences campus; participants will be remunerated $100 for participation.

C.5.3. Procedure overview. Participants will complete an informed consent and provide a saliva sample, a urine sample, and/or a blood sample via finger stick for cotinine assessment. Participants will be asked to include their social media contact information. This information will only be used to contact participants if they change their email address and/or phone number. We will not use this information to follow participants or collect information about them. Participants will view a video tutorial explaining the controlled e-cigarette administration procedure.

Figure 1. Pilot Study Experimental Session

Note. Pre-Ad. = Pre e-Cigarette Administration assessment; Post-Ad. = Post e-Cigarette Administration; Pre-Rest = Pre Rest Period assessment; Post-Rest = Post Rest Period assessment. All assessments include subjective and physiological measures.
Study Protocol and Statistical Analysis

(see C.5.4). We will use a computerized digital slideshow to present images of the product packaging informing subjects that the image depicts the product they will be administering. We will then cue subjects when to inhale and exhale from the device with the image displayed until the next product exposure. In between e-cigarette administrations participant characteristics will be assessed and there will be a short rest period (see C.5.7). Each trial will be presented in random order.

C.5.4. Product administration. Based on prior e-cigarette puffing topography data and our past work, this procedure will have a brief preparation interval, an inhalation interval, a brief hold interval, and an exhale period. Subjects will complete this procedure for each condition. Participants will be shown a video on how to self-administer the e-liquid by first using an e-liquid with 0mg nicotine and without flavor. During the study visit for experiments testing effects of flavor and nicotine, participants will vape 20 different e-cigarette liquids. They will receive 10 different flavors of e-liquids in two nicotine solutions (free base and salted), order randomized. During the study visit for experiments testing effects of packaging, participants will vape 9 different e-cigarette liquids twice (once in youth-oriented packaging and once with regular packaging) in free-base or salt, order pseudorandomized to prevent back-to-back administrations of the same e-liquid. Participants will not be told which e-liquid combination they received. The use of deception is necessary to prevent participants from developing expectations based on the flavor/nicotine solution. After each administration, subjects will rate appeal and sensory effects (see C.5.8), and then may be given the opportunity to wash out their mouth with water and complete the next administration. In our past work subjects completed up to 40 administrations (i.e., conditions) without fatigue or reporting taste saturation. At the end of the study visit, participants will be told that they received 10 different flavors of e-liquids presented in two nicotine solutions. Due to the number of different e-liquids, the order of self-administration will not be disclosed.

C.5.5. Device and e-liquids for product characteristics manipulation. We will use popular, commercially available devices (e.g., Suorin) and e-liquids manufactured by leading domestic providers.

C.5.6. Package Manipulation. During the study visit for experiments testing effects of packaging, images will either have: (1) Plain Label, with the name of flavor only (e.g., ‘peach’); (2) Youth-Oriented Name Label, with the product name (e.g., ‘peach gummy bear’). We will create a Youth-Oriented Name Label and Plain Label, resulting in nine sets of duplicate matched labels – one for each flavor.

C.5.7. Participant Characteristic Questionnaires. We will collect information on demographics and health history to describe the sample. The Pennsylvania State University Electronic Cigarette Dependence Index (PSECD) smoking history questionnaires (SHQ), Wisconsin Inventory of Smoking Dependence Motives (WISDM), Wisconsin Inventory of Smoking Dependence Motives E-Cigarette (WISDM-EC) and Vaping History Questionnaire (VHQ) will assess e-cigarette and other tobacco product use characteristics, including preferred e-cigarette flavor, device type, wattage, menthol smoking (for smokers), history of e-cigarette use and smoking, and heaviness/frequency of e-cigarette use and smoking. The Fagerström Test for Cigarette Dependence (FTCD) will assess combustible cigarette dependence. Additional data on depressive symptoms (Center for Epidemiologic Studies Depression Scale), drug use (Drug Abuse Screening Test), and Alcohol Use Disorders (AUDIT) will also be collected for use as covariates and for investigator-initiated secondary analysis.

C.5.8. Objective Coding of E-cigarette Products used by Vapers. The young adult vapers will be instructed to bring their device and e-liquid bottles. Using a classification system from our previous work, devices and e-liquids will be coded by staff (e.g., device: first vs. second vs. third generation vs. pod-mod, modifiability, resistance, voltage, e-liquid nicotine concentration, flavoring type, marketing approach: cartoon vs. not). We will also use the Coil Master to determine device wattage. Data will be used to evaluate the validity of self-report measures on wattage for use in future studies.

C.5.9. Assays of Product Constituents. The nicotine concentration, characterizing flavors (i.e., flavoring chemicals), PG/VG ratio, and other constituents of the e-liquids used in this study will be authenticated by the manufacturer and/or the Nicotine and Tobacco Product Assessment Shared Resource (NicoTAR) at the Roswell Park Cancer Institute.

C.5.10. Self-report Appeal and Sensory Effects Measures. Following a similar protocol to that which we’ve used previously, after each administration, participants will respond to questions assessing the appeal of the preceding product: 1) “How much did you like the e-cigarette?” (“Not at all” - “Extremely” anchors); 2) “How much did you dislike the e-cigarette?” (“Not at all” - “Extremely” anchors); 3) “Would you use this e-cigarette again?” (“Not at all” - “Definitely”); 4) “How sweet was the e-cigarette?” (“Not at all” - “Extremely”); 5) “How smooth was the e-
will undergo labeling, and then cue subjects when to inhale and exhale from the e-cigarette. After analysis is complete, original recordings will be disposed of confidentially. Identified with only the participant’s number. Original recordings will be stored on our secure server with other data.

 Participants will then be informed to abstain from all tobacco products beginning at the night before the experimental session. CO will be performed one experimental session employing a factorial design. After overnight tobacco product deprivation, participants will self-administer an e-cigarette product from the assigned condition(s). Then, participants will complete a self-report and physiological measures as well as behavioral economic tasks that test the participant’s choice of earning money to delay initiation and continued use of tobacco product deprivation, participants will self-administer an e-cigarette product from the assigned condition(s). Then, participants will complete a self-report and physiological measures as well as behavioral economic tasks that test the participant’s choice of earning money to delay initiation and continued use of: (1) The sampled e-cigarette product (abuse liability); or (2) Their own brand cigarettes (ability to resist smoking; current smokers only).

Power Calculations: For Aim 1, based on an estimated interaction effect from our preliminary data ranging from d=.25 to d=.40 and an intraclass correlation coefficient due to subject of .04, while assuming a modest effect estimate in the range above, we would have 90% power to detect effects, with N≥20 per group.

C.6. Aim 2: Abuse Liability and Ability to Resist Smoking.
C.6.1. Study Design. Participants will first complete a baseline session to confirm eligibility (see C.6.3). Then, participants will complete one experimental session (see C.6.4) employing a factorial design. After overnight tobacco product deprivation, participants will self-administer an e-cigarette product from the assigned condition(s). Then, participants will complete a self-report and physiological measures as well as behavioral economic tasks that test the participant’s choice of earning money to delay initiation and continued use of: (1) The sampled e-cigarette product (abuse liability); or (2) Their own brand cigarettes (ability to resist smoking; current smokers only).

C.6.2. Participants, Recruitment, Eligibility Criteria, and Compensation will be identical to Aim 1, with the exception that participants will be paid a separate fee of $20 for completing the baseline visit.
C.6.3. Baseline Session Procedure. After phone screen, subjects will attend the baseline visit involving informed consent and a saliva sample, a urine sample, and/or a blood sample via finger stick for cotinine assessment and CO. Participants will be asked to include their social media contact information. This information will only be used to contact participants if they change their email address and/or phone number. We will not use this information to follow participants or collect information about them. Eligible participants will then complete participant characteristic questionnaires and product coding (see C.5.7 and C.5.8). Subjects will view a controlled administration tutorial that they will use in the experimental session and practice with the study device. Participants will then be informed to abstain from all tobacco products beginning at the night before the experimental session.

C.6.4. Experimental Session Procedure. At the beginning of each session, CO, and salivary or urinary cotinine will be performed. Participants will first undergo a pre-administration assessment, during which they will complete self-report and physiological measures (see C.6.7). Then, a standardized administration will occur (see C.6.5), followed by the post-administration assessment. Subjects will then begin the respective product/choice task, followed by a rest period and dismissal. At the completion of the final experimental session, participants will be debriefed and informed about the purpose of the study. Vaping and smoking portions of the sessions may be recorded using digital video, for subsequent analysis of smoking and vaping behavior. Video recordings will be identified with only the participant’s number. Original recordings will be stored on our secure server with other electronic data. After analysis is complete, original recordings will be disposed of confidentially.

C.6.5. E-cigarette administration. Administration will occur by using the digital slideshow to present the product labeling, and then cue subjects when to inhale and exhale from the e-cigarette device (see C.5.4). Participants will undergo 5-15 cycles (i.e. puffs) to approximate the nicotine in cigarettes for participants who smoke (see 8

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C.3) or complete 2 puffs to provide a 'sample' of the product.

C.6.6. E-cigarette Device and Liquids and Product Labeling. See C.5.5 and C.5.6.

C.6.7. Baseline Session Measures: Characteristics and Product Coding. See C.5.7 and C.5.8.

C.6.8. Collection of blood specimens. To gauge level of nicotine delivered throughout the study paradigm, a subset of participants will be asked to provide blood specimens before and after the behavioral tasks. We will obtain two 6mL blood (plasma) specimens during each experimental session for measurement of plasma nicotine. Certified nurses/phlebotomists from USC Diabetes & Obesity Research Institute (DORI) will collect and process all blood samples (see BUA).

C.6.9. Experimental Session Subjective and Physiological Measures. Participants will complete subjective measures at pre and post assessment, with subjective measures instructing response based on how they feel “right now.” The Cigarette Rating Scale (CRS)\(^67\) and an adapted version of the CRS for vaping will assess the psychological reward of each e-cigarette condition. The self-report appeal and sensory effect measures will be amministered (see C.5.10). The 10-item Positive Affect Negative Affect Schedule (PANAS)\(^68\) will be used to measure positive and negative affect. The 10-item Brief Questionnaire of Smoking Urges (QSU)\(^69\) will assess desire, intention, urge, and need to smoke cigarettes, with a modified version to assess vaping urges used in the vapers. The Minnesota Nicotine Withdrawal Scale (MNWS)\(^66\) measures 11 nicotine withdrawal symptoms on 6-point scales, the Tobacco Craving Questionnaire (TCQ)\(^91\) will assess four dimensions of tobacco craving (i.e., emotionality, expectancy, compulsivity, purposefulness), the Wisconsin Smoking Withdrawal Scale (WSWS)\(^62\) will assess the severity of seven individual withdrawal symptoms (i.e., anxiety, anger, hunger, concentration problems, craving, sadness, sleep) and the state version of the Snaith-Hamilton Pleasure Scale (SHAPS)\(^93\) will assess current hedonic responsivity. Heart rate and blood pressure will be taken with a digital sphygmomanometer, and CO levels will be assayed with a Bedfont Scientific Smokelyzer® breath CO monitor. Vaping effects questionnaire, a variant of the cigarette evaluation questionnaire,\(^94\) will be used to assess subjective rewarding effects of the product at post-administration.

C.6.10. Behavioral Choice of Vaping vs. Money (Abuse Liability). This task utilizes behavioral-economic principles to measure participants' choice between two competing reinforcing agents, vaping vs. money, was derived to parallel the smoking measure\(^66\) and exhibits good convergent validity. The task begins with the delay period, in which participants will be presented with the e-cigarette used during the sampling procedure. Participants are instructed that they may begin vaping at any time over the next 50 minutes, but for every 5 minutes that they delay vaping, they will earn a value ~ $0.20 - $1 (dependent on piloting) that will be paid at the end of their visit. The self-administration period begins when participants indicate that they wish to initiate vaping (or at the end of 50 minutes for participants who chose not to vape during the delay period). Here, subjects are instructed they may vape as much as they wish over the next 60 minutes, and for each 5-minute period they vape, $0.20- $1 will be subtracted from an initial total amount. Following the self-administration period, participants will enter a rest period of no procedures, which prevents intentional avoidance of vaping due to impending opportunity to vape at session end, and therefore maximizes vaping choices. The key outcome is the number of minutes delayed (reflected by subtracting from 50 so that higher scores indicate more abuse ability), number of vaping periods purchased (0-12), binary indicators (delay all 50 minutes: no=1 vs. yes = 0), and vaping during self-administration (yes = 1 vs. no = 0). Our previous research has demonstrated that these price points are sensitive to manipulations.\(^95\)

C.6.11. Behavioral Choice of Smoking vs. Money (Ability to resist smoking; smokers only). This task, which we and others have used extensively,\(^66,95\) utilizes the parameters as above. However, participants are attempting to delay initiation of smoking their own-brand cigarettes for up to 50 minutes, at the equivalent per every 5 minutes delayed; during the self-administration portion, participants also get deducted the equivalent per cigarette smoked. Primary outcomes parallel those above (e.g., delay 0-50; all 50 minutes: yes=1, no=0).

C.6.12. Data Analysis. Aim 2 analysis will use the same strategy as Aim 1, with the exception that all variables are between-subjects, with one data point per subject. Thus, we will use a general linear modeling framework. For Aim 2, outcome variables will be reflected such that higher scores indicate greater motivation to vape for young adult vapers, and lower motivation to smoke (i.e., greater ability to resist smoking) for middle-age/older adult smokers. Significant Group (e.g., non-smoking vapers vs. smokers) × Flavor, Group × Nicotine formulation, and Group × Packaging interaction effects may be interpreted as a disproportionate impact of respective domain of product diversity on e-cigarette abuse liability for young adult vapers, relative to the ability to resist smoking for middle-age/old smokers. The vaping subjective rewarding effect measure, as a supplemental outcome, will
be analyzed in the same fashion. Other analyses, including studies of gender interactions for exploratory purposes, will use the same strategies as C.5.10, applied to the current between-subject design. To test effects on intermediate outcomes with pre-post designs (e.g., withdrawal, urge to smoke/vape), the same strategy will be used for controlling pre-administration scores.

**Power analysis:** Given anticipated effect estimates likely smaller than that of Aim 2, behavioral outcomes are typically more prone to error and ability to isolate pair-wise condition effects interaction contrasts will require larger Ns per factor level, we can assume a modest effect size of $d=.25$. We would need to sample 712 participants to obtain 80% power.

C.7. Timeline. In the past 2 years, USC-HEAL has recruited 37 subjects per month for studies similar to those proposed herein, with a 12% attrition rate and 25% ineligibility rate. Given these parameters, Aim 1 would require approximately 18 months and Aim 2 would require 33 months to complete. With 4 months for startup and completion of the study pilot, 2 months for setup between Aims, and 3 months for analysis and write-up, this is estimated to be a 60-month project.
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