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Evaluating Concomitant Use of Very Low Nicotine Content Cigarettes and E-cigarettes Among Daily and Non-Daily Smokers

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A. SPECIFIC AIMS

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) provides the FDA with authority to limit the nicotine content of cigarettes, which could reduce cigarette reinforcement and lead to reduced abuse liability. Recently, the FDA announced its intention to regulate the e-cigarette (e-cig) market. At this time, we have very little information on how such changes in the tobacco marketplace, specifically with e-cigs, will affect smoking behavior, nicotine reinforcement, and the abuse potential of dual product use. The *objective* of this study is to model abuse liability in a market in which the level of nicotine in combustible cigarettes has been lowered to meet a potential regulatory standard, but one in which an alternate source of nicotine in e-cigs is also available. The *significance* of this proposal is that it will provide the FDA with critical information about the effects of dual use of very low nicotine content cigarettes (VLNCC) and e-cigs with differing levels of nicotine on nicotine abuse liability, as measured by nicotine compensation, product use and liking, relative reinforcing efficacy (RRE), and multi-modal assessments of withdrawal, craving, affect and satisfaction, among both daily (DS) and intermittent (ITS) smokers in the lab and in their natural environment. The coexistence of these products raises questions about whether the potential public health benefit of VLNCC at reducing nicotine abuse liability might be offset by the concurrent use of e-cigs. The *positive impact* of this study will be to provide scientific information on the nicotine abuse liability impact of reducing nicotine in combustible cigarettes to a non-reinforcing level within a dual product use environment, which can be used to inform tobacco regulatory strategies designed to promote the public health. The *innovativeness* of this study is our focus on the nicotine abuse liability of dual use by both DS and ITS, and our use of a multimodal approach to the measurement of abuse liability constructs, including the use of EMA, given that little is known about the effects of dual use on these abuse liability constructs in the natural environment. The *value added* feature of this study is it complements and extends the findings of existing TCORS involving VLNCC (U54DA031659; PI's Donny & Hatsukami) and e-cigs (P50DA036105; PIs Eissenberg & Balster), and uses dosing based on findings from those projects. Additionally, this protocol will evaluate, on an exploratory basis, the dual use potential of the most popular e-cig device on the U.S. market [1], the 4th generation JUUL "pod mod" system (JUUL Labs Inc., San Francisco, CA), which now comprises over 75% of the U.S. market [2].

Participants will be up to 380 smokers made up of a combination of daily (DS) and intermittent (ITS) non-treatment-seeking adult smokers. Participants will smoke their usual brand (UB) during Phase 1 (Baseline; week 1) and will exclusively smoke the VLNCC during Phase 2 (weeks 2-4). During phases 3 (weeks 5-7) & 4 (weeks 8-10), smokers will be instructed to freely use any combination of assigned VLNCC and e-cigs (VLNCC+ECIG). All subjects in this arm will receive a 2nd generation eGo electronic cigarette in two e-cig doses (ECIG-Hi [36 mg/ml] and ECIG-Lo [8 mg/ml]), with dose order counter- balanced across phases 3 and 4. Additionally, in a second arm, at least 80 daily smokers will be randomized to the JUUL arm (VLNCC for phase 2 and combined VLNCC+JUUL-Hi or -Lo for phases 3 & 4). All participants in the JUUL arm will receive both e-cig doses (JUUL-Hi [JUUL 5%; 59 mg/ml nicotine] and JUUL-Lo [JUUL 3%; 35 mg/ml nicotine]), with order counter-balanced across phases 3 and 4. For all groups and phases, we will assess nicotine compensation, in the form of total nicotine equivalents (TNE) and minor alkaloids (MA; i.e., anabasine, anatabine, and nornicotine), product-specific use and liking (i.e., implicit attitudes, perceived harm, satisfaction), and RRE (i.e., purchase task indices). Participants will attend 5 sessions and will complete questionnaire and smartphone assessments of withdrawal, craving, affect, product satisfaction, and product use. We propose the following *specific aims* and *hypotheses*:

Aim 1: To characterize the effects of switching to VLNCCs plus ECIG-Hi or ECIG-Lo nicotine doses on abuse liability among daily and intermittent smokers. Our primary measures of abuse liability will be CPD (product use) and nicotine equivalent (TNE) levels

(nicotine compensation). We hypothesize that compared with the VLNC+ECIG-Lo phase, smokers will show decreased CPD and TNE levels during the VLNC+ECIG-Hi phase.

Aim 2 (Exploratory): To explore the effects of switching to VLNCCs plus ECIG-Hi or ECIG-Lo nicotine doses on abuse liability using biochemical measures of product use, compensation, and toxicant exposure, and self-reported measures of withdrawal, craving, affect, and satisfaction. On an exploratory basis, we will examine the differences of ECIG dose (VLNC+ECIG-Lo vs. VLNC+ECIG-Hi) on additional measures of abuse liability, including ECIG puff count, withdrawal, craving, negative affect, minor tobacco alkaloid (MA) levels, acrolein DNA adduct levels, expired CO, RRE (i.e., purchase tasks), and liking (implicit attitudes, perceived harm, product satisfaction ratings).

Aim 3 (exploratory): To explore the effects of switching from usual-brand cigarettes to VLNCCs, and from VLNCCs to VLNCC+ECIGs on measures of abuse liability. On an exploratory basis, we will examine potential changes in the abuse liability measures from Aims 1 & 2 between the UB cigarette and VLNCC only phases, and between those phases and the dual-use phases (VLNC+ECIG-Lo and VLNC+ECIG-Hi).

Aim 4 (exploratory): To characterize the effects of dual use of VLNCC and JUUL ECIGs on abuse liability. On an exploratory basis, we will examine the differences in measures of abuse liability between the two phases of dual-use (VLNC+JUUL-Lo vs. VLNC+JUUL-Hi) among participants assigned to the JUUL ECIG arm.

B. SIGNIFICANCE AND INNOVATION

Significance

In 2009 Congress granted the FDA authority over non-medicinal nicotine products for the first time [3], and created the Center for Tobacco Products (CTP) to oversee them. As part of this act, the FDA was provided with substantial funds to facilitate tobacco regulatory science (TRS) research that would inform their future regulatory actions. The FDA CTP has identified eight priority areas, including research focused on chemistry & engineering, toxicity, addiction, health effects, behavior, communications, marketing influence, and impact analysis, to help inform future regulation of tobacco products on the market [4]. The FDA has channeled most of those funds through NIH mechanisms to fund research projects of interest. Many of these FOAs explicitly solicited research designed to evaluate whether noncombustible nicotine products, such as electronic cigarettes, are potentially safer alternatives to smoking combustible cigarettes. For example, the purpose of PAR-18-220, which funded one of our active electronic cigarette protocols (2018-0794), states "… is to accelerate research evaluating electronic cigarettes (e-cigarettes, electronic nicotine delivery systems, ENDS) as a potential means of reducing the risks associated with combustible tobacco use." This protocol, and our protocols that we describe below, have all had this objective of investigating potential approaches to moving non-treatment-seeking combustible cigarette smokers away from a product that results in the death of over 1300 Americans each day [5].

The significance of this project is that it will provide the FDA with critical information on the effects of dual use of combustible and e-cigarettes (e-cigs) on nicotine abuse liability, as measured by nicotine compensation, product use and liking, relative reinforcing efficacy (RRE), withdrawal, craving, affect, and satisfaction. Our objective is to model abuse liability in a market in which the nicotine content in combustible cigarettes has been reduced to meet a proposed regulatory standard (very low nicotine content cigarettes; VLNCC), but one in which e-cigs provide an alternative source of nicotine. E-cigs are growing rapidly in popularity [6], and despite the intention of FDA to regulate them, there is little information on the interactive effects of VLNCCs and e-cigs on issues surrounding abuse liability. An important consideration for

regulation should be the level of nicotine available in e-cigs, as this could have an impact on nicotine abuse liability. In a dual use environment the availability of varying nicotine doses in e-cigarettes can be expected to affect nicotine compensation, product liking, relative reinforcing efficacy (RRE), withdrawal, craving, and affect in comparison to VLNC cigarettes alone. A sufficiently high level of available nicotine in an e-cig might persuade some smokers to reduce use of combustible cigarettes substantially, but it would be crucial to have information on the possible trade-off between reducing dependence on smoking on one hand, and potentially increasing dependence on e-cigs, on the other. Moreover, not all smokers might be affected by the combination of VLNCCs and e-cigs in the same way. The evidence suggests that regulation of nicotine self-administration by daily (DS) and non-daily/intermittent (ITS) smokers, who represent up to a third of US adult smokers [7], might be driven by different motives. DS may smoke more often to avert symptoms of withdrawal, including negative affect while ITS may be more inclined to maximize satisfaction/positive reinforcing effects of nicotine [8]. The effective nicotine dose in e-cigs might have different implications for these two groups. For example, DS might use VLNCCs and e-cigs in different combinations, depending on dose, in an attempt to reach some target minimum nicotine level, whereas ITS might combine products or even substantially shift to e-cigs to maximize nicotine exposure on a per use basis, as they do now with conventional cigarettes [8]. The potentially different effects on these doses on key indices of nicotine abuse liability among ITS and DS will be assessed using a multi-modal approach to the measurement of withdrawal, craving, affect and reinforcement (satisfaction). Our study provides progressively more sensitive assessments of each of these constructs that range from traditional measures (questionnaires filled out weekly), to smartphone daily diary (patients overall assessment of the day), to real-time measures captured through smartphone EMA.

Adding to the overall significance of the present project is the value added to two currently funded FDA TCORS, separately examining VLNCCs (U54DA031659; Donny & Hatsukami) and e-cigs (P50DA036105; Eissenberg & Balster). The current study leverages results from current analyses of these projects to inform our design and maximize the scientific and regulatory value gained from this study. The current study is not a replication of these studies, but rather is a logical extension of their results to a real-world model of potential tobacco policy changes they have been designed to inform. Results from the U54 suggest that among several nicotine doses (0.8 mg-0.03 mg/cigarette=17.7 mg-0.4 mg/g tobacco) in VLNCCs, the 0.03 mg nicotine dose (0.4 mg/g tobacco) results in smoking the fewest cigarettes per day, lowest total nicotine equivalents (TNE, the sum of nicotine, cotinine, 3'-hydroxycotinine and their glucuronides), and lowest nicotine dependency scores, with no change in expired carbon monoxide (CO) concentrations (i.e., no compensatory smoking) or indicators of nicotine withdrawal [9]. This dose is being used as the minimally acceptable VLNCC dose in two other projects in this U54, one involving a comparison of gradual vs. abrupt transition from a conventional to a VLNCC, and another investigating the transition to VLNCCs among schizophrenic smokers. Based on this work, we selected the 0.03 mg nicotine VLNCC for this study. In addition to Drs. Donny, Hatsukami, and Eissenberg from these TCORS, we are joined by co-investigator Dr. Murphy, who will provide assessment of biomarkers of exposure common to this application and the U54, including TNE and minor tobacco alkaloids (MA). *Assessing these constituents during dual product use will add to the body of scientific information on VLNCC and e-cigarette use and compensation, which would inform FDA policy beyond what has been done in the U54 using VLNCCs alone.*

As part of the other P50 noted above, Dr. Eissenberg has conducted extensive testing of e-cig hardware and nicotine solutions in order to determine the optimal product configuration that will deliver specified doses of nicotine to the user. He has selected a commercially available e-cig configuration (eGo battery and 510 XL cartomizer) that when supplied with a nicotine solution of 36 mg/ml (verified by gas chromatography mass spectrometry; GCMS), *provides*

nicotine levels in the plasma similar to conventional cigarettes. This e-cig configuration will be used in a large clinical trial planned in this TCORS to evaluate the effects of e-cigs on reducing use of conventional cigarettes. We will utilize the same e-cig configuration and nicotine solutions yielding both high (36 mg/ml) and low (8 mg/ml) nicotine concentrations (see preliminary studies), in our examination of dual use with VLNCCs.

Thus, the current study extends the generalizability and scientific value of both TCORS by modeling the abuse liability effects of a market in which the level of nicotine in combustible cigarettes has been lowered to meet a potential regulatory standard, but one in which an alternate source of nicotine in e-cigs is also available. *This scenario is possible as we move towards regulation of nicotine levels across products and it could be argued that this approach might be used to drive smokers away from combustible tobacco and towards a potentially less toxic nicotine delivery system.*

Innovation

The innovations of this project are that: (1) we will be the first to evaluate the potential dual use of VLNCCs and e-cigs among intermittent smokers (ITS), in addition to daily smokers (DS); and (2) we take a multi-level approach to assessing abuse liability by measuring: a) nicotine compensation using TNE, MA, and expired CO; b) product-specific measures of liking (i.e., implicit attitudes, perceived harm, and satisfaction); c) product-specific RRE (i.e., purchase task valuation); d) single and dual product use as measured by CPD, ECIG (cartridge weight puff counter); e) withdrawal, craving, affect, and satisfaction (reinforcement) using progressively more sensitive instruments that range from traditional measures (questionnaires filled out weekly) to the smartphone daily diary (patients overall assessment of the day), to real-time measures captured through smartphone EMA. These EMA data, in particular, will enhance our ability to identify differences between DS and ITS, and participants' preferences for dual use of high- and/or low-dose e-cigs with VLNCCs. The use of EMA is innovative because so little is known about the effects of dual use on abuse liability measures in the natural environment. The *positive impact* of this study will be to provide scientific information on the relative importance of e-cig dose, nicotine compensation, product liking, RRE, withdrawal craving, affect, and satisfaction in a dual product use environment, which can be used to inform both tobacco regulatory strategies (e-cigarette dose) and future studies focusing on reducing nicotine dependence.

C. APPROACH

Justification and Feasibility

Review of Relevant Literature

Abuse liability is a multimodal construct that can be measured in reduced exposure products. The FDA typically ascertains a drug product's abuse liability as part of determining a product's potential health risks. A product's abuse liability is shaped by its pharmacology, pharmacokinetics, adverse effects, and environmental factors (e.g., social acceptability, price, marketing exposure) [10]. To measure abuse liability, Carter and colleagues [10] describe several domains that can be assessed, including (a) drug discrimination (e.g., identifying threshold doses), (b) acute dose-effect comparisons (e.g., physiological and cognitive effects), (c) suppression of withdrawal and craving, (d) self-administration (e.g., progressive-ratio breakpoints, behavioral economic procedures), and (e) choice procedures (e.g., dual use choice). These approaches have been adapted to studying the abuse liability of VLNCC [11] and e-cig [12] products.

VLNCC smokers may seek to maintain optimum levels of nicotine to facilitate reinforcement. Cigarette smoking's abuse liability is primarily driven by the presence of

nicotine, the primary psychoactive constituent of tobacco smoke. Nicotine directly activates brain reward circuits [13] that enhance self-administration [14] and stimulates multiple neurotransmitter systems throughout the brain that play a critical role in modulating affect, attention, and cognitive performance [15–18]. Repeated nicotine use leads to dependence, during which smoking may be triggered by the presence of aversive withdrawal symptoms that emerge when brain nicotine levels decrease [19, 20] and/or the presence of motivationally relevant cues associated with craving, stress, and particularly negative affect [21–23]. Avoidance of these conditions prompts further nicotine use, which results in the compulsive pattern of nicotine-seeking behavior that characterizes the addictive process [18, 24, 25]. Smoking behavior is thought to reflect an attempt at maintaining an "optimum" level of nicotine in the brain that maximizes its subjective effects (both liking and wanting) and minimizes withdrawal symptoms [26]. This is supported by studies that have varied the nicotine yield of cigarettes. The typical nicotine yield of commercially available cigarettes is approximately 0.8 mg/cigarette [27]. When this is reduced to levels as low as 0.3 mg, some smokers compensate for the reduced nicotine yield by smoking more cigarettes or by extracting more nicotine per cigarette by increasing puff volume and duration [11, 28–31].

For those who smoke daily, it is thought that a minimum level of nicotine is required to maintain dependence. Below this minimum, brain reward circuitry may not be sufficiently activated and over time, nicotine-self administration may undergo extinction [32]. Thus, a promising regulatory/treatment approach for reducing the abuse liability of cigarettes may be lowering nicotine content to a level below what is required to maintain dependence [26]. In the past, commercially available VLNCCs typically had nicotine levels below 0.1 mg. When transitioned to these VLNCCs, smokers may initially compensate for the nicotine loss via increased smoking [33], but over time the total VLNCCs consumed is expected to decrease because nicotine levels may be insufficient to reinforce continued high levels of smoking [11, 30, 31, 34].

Although short-term laboratory studies using "de-nicotinized" cigarettes (~.07 mg nicotine) have indicated some beneficial effects on withdrawal, craving [35, 36], and reinforcement [37], most studies have shown that these cigarettes are preferred less [38], produce fewer positive subjective effects [39], provide less satisfaction [40], provide less reward [11], and alleviate fewer withdrawal symptoms [41] than "normal" cigarettes. In addition, none of these previous studies used the highly sensitive EMA approach to assess these construct’s in real-time. In an environment where VLNCCs are the only available nicotine product (i.e., as a function of new FDA regulations), new smokers experimenting with tobacco products would presumably not become addicted and current smokers could be persuaded to eventually quit smoking as a result of extinction. *However, having an alternative means of obtaining nicotine, such as e-cigs, might have an impact on the success of regulatory (and treatment) strategies aimed at reducing the abuse liability of combustible cigarettes.*

One possibility is that smokers will continue to use VLNCCs to obtain the conditioned-reinforcing effects of smoking, including taste, sensorimotor stimulation [11], and perceived cognitive enhancement [42, 43]. However, because lower nicotine content is expected to produce far less robust changes in affect and cognitive performance than higher nicotine content [42, 43], some smokers might use e-cigs to offset (supplement) the reduction posed by VLNCCs, retaining the primary reinforcing effects of nicotine and avoiding the emergence of withdrawal symptoms. In this case, brain nicotine levels would remain above the minimum level required to maintain addiction, thus maintaining abuse liability. The proposed study will address this important psychopharmacological question, and will provide evidence to inform decision-making about regulating the nicotine levels of e-cigs.

E-cig prevalence is increasing and is subject to dual use. E-cigs (also known as electronic nicotine delivery system; ENDS) were introduced in the US in 2007. Public awareness among adults had grown to over 75% by 2012, and 88% of current smokers were aware of them [44]. The technology is rapidly changing and many electronic nicotine delivery systems are available [45].

In a recent and comprehensive survey assessing use, prevalence, and demographics, Zhu and colleagues [44] found that the prevalence of ever and current use of e-cigs was highest among adults who were current smokers (32.2% & 6.3%, respectively) and recent former smokers (26.8% & 6.1%, respectively), but negligible among long-term former smokers (2.4% & .2%, respectively) and never smokers (1.0%, & 0%, respectively). In a study of nearly 6,000 people from the US, UK, Canada, and Australia, Adkison [6] found that nearly half of the sample were aware of e-cig products, and the prevalence of trying e-cigs was higher among younger, nondaily smokers with a higher income who perceived such products as less harmful than traditional cigarettes. Current e-cig use was highest among nondaily and heavy smokers (>20 CPD) [6]. Dual use appears to be most common among current smokers who were considering quitting in 6 months [46], as well as among young adult smokers aged 18-24 [47]. A sizeable number of e-cig users continue to smoke combustible cigarettes [46, 48], with nearly half reporting e-cig use in situations where they can't smoke [44]. Most smokers who report using e-cigs in the last 30 days do not report using them daily [44]. In a recent internet survey, dual users reported nearly a 50% reduction in consumption of combustible cigarettes from baseline, although such changes were not maintained at 1 year [49].

These results suggest considerable heterogeneity in patterns of dual use and highlight the importance of assessing both daily and nondaily smokers. The fact that heavy smokers and non-daily smokers are both inclined to use e-cigs offers some support for our contention that these groups might be differentially responsive to e-cig dose. Given the broad differential in their normal level of nicotine exposure from smoking typical cigarettes, intermittent use of higher dose e-cigs may provide an approach for DS to compensate for the changes nicotine level brought about by using the VLNCCs, while ITS may be able to accomplish the same objective using either high or low dose e-cigs, while potentially substituting e-cigarettes for VLNCCs. The current study will examine several factors influencing dual use patterns, including level of current smoking, ECIG dose, liking, withdrawal, craving, affect and reinforcement by DS and ITS, and will examine potential effects of dual use on nicotine compensation.

E-Cig nicotine pharmacokinetics: Becoming more like combustible products. Conventional combustible cigarettes possess many characteristics that facilitate nicotine dependence, including fast-acting pharmacokinetics associated with nicotine delivery [50], reinforcement-enhancing constituent chemicals (e.g., minor alkaloids, MAO inhibitors) [51, 52], and conditioned non-nicotine stimuli (e.g., environmental cues; airway sensations) [53]. While new generation e-cigs have been found to increase blood plasma nicotine levels by up to 72% more than first-generation small e-cigs [54], current studies suggest that most e-cigs may not be capable of increasing blood plasma levels as rapidly as combustible tobacco cigarettes [55, 56]. Farsalinos and colleagues [54] found that, after 5 minutes of use, an 18 mg/ml nicotine e-cig delivered 25 to 33% of the blood nicotine levels as smoking one combustible tobacco cigarette. However over a period of 30-75 minutes, blood plasma nicotine may become comparable to those attained by smoking tobacco cigarettes [54, 57].

The e-cig continues to evolve rapidly through improved technology, with higher capacity batteries and higher nicotine content solutions affording greater nicotine exposure to the user. It is likely that more smokers will be attracted to e-cig use as they become more like combustible tobacco in nicotine delivery. We believe that understanding the differences in multiple areas of concern (e.g., nicotine compensation, product liking, pattern of use, withdrawal, affect, craving,

and satisfaction) between high and low dose nicotine in e-cigs is an important consideration for regulation. Our co-investigator, Dr. Eissenberg, has provided the ideal e-cig platform for studying these differences, having done extensive preliminary work on the engineering of e-cigs and the concentration of nicotine in the nicotine solution, which in the right combination can produce blood levels of nicotine similar to those achieved with conventional cigarettes (see preliminary studies). This study will use that platform and will be the first to assess compensation, liking, and patterns of use, and to conduct multi-modal assessments (questionnaires, diary, EMA) of withdrawal, craving, affect and reinforcement, by DS and ITS, using e-cigarettes capable of delivering variable doses of nicotine to the user.

Newer Generation IV e-cig products with higher nicotine content, such as JUUL, may be more reinforcing to smokers. Several studies that have surveyed the real-world effectiveness of using e-cigs to aid smoking cessation attempts have found e-cigs may reduce CC consumption or promote abstinence, although results are mixed, and can result in dual use of both products [58–62].The reason that smokers may not be able to switch to exclusive e-cig use may be due to many commercially available e-cigs not being able to deliver as much nicotine as CCs. While 2nd generation e-cigs have been found to increase blood plasma nicotine levels compared to 1st generation e-cigs [54, 63], studies suggest that most e-cigs may not be capable of increasing blood plasma levels as rapidly as smoking CCs [55, 56]. Most e-cig users reported using between 4 mg/ml and 24 mg/ml nicotine concentrations [64]. Farsalinos and colleagues [54] found that, after 5 minutes of use, an 18 mg/ml nicotine e-cig delivered 25 to 33% of the blood nicotine levels as smoking one CC, although blood plasma nicotine may become comparable to those attained by smoking CCs over a period of 30-75 minutes [54, 57]. Preliminary data suggest that higher nicotine concentrations than are typically consumed by e-cig users may be necessary to produce CC-comparable nicotine pharmacokinetics. For example, e-cig-naive smokers were found to achieve CC-comparable nicotine levels with 36 mg/ml e-cig nicotine concentrations, but not at lower concentrations (8 or 18 mg/ml) [65]. Other preliminary data suggest that high nicotine-dose JUUL e-cigs (i.e., 59 mg/ml) produce nicotine pharmacokinetics (i.e., C_{max} and T_{max}), satisfaction, and craving reduction comparable to CCs among adult CC smokers [66]. Thus, we believe that offering smokers high nicotine-dose e-cigs, such as JUUL, may promote their use and acceptability, and reduce the use of CCs.

Intermittent non-daily smokers may be more amenable to low (and high) dose e-cigs. Non-daily or intermittent smokers (ITS), a growing segment of the smoking population (approximately 33%), have been defined as those who smoke between 4 and 27 days per month, with no restrictions on the number of cigarettes smoked on smoking days [67–69]. Individuals who are initiating smoking (i.e., those who are under 21 years of age or who have smoked for fewer than 3 years) are not considered ITS, nor are smokers who are unable to smoke daily due to economic constraints [70]. Some ITS have never been daily smokers ("Native" ITS), while others are former daily smokers (DS) who have reduced their smoking rate ("Converted" ITS). In both cases, ITS show signs of nicotine dependence [71], report craving for cigarettes [72–74], and show conditioned responses to cigarette cues [75–77]. ITS also have difficulty quitting smoking, with long-term abstinence rates as low as 18% [78]. Moreover, ITS also suffer from the long-term health consequences of smoking, such as cardiovascular disease [79]. Thus, it is important to study how ITS, as well as DS, might be affected by both VLNCCs and e-cigarettes since they too will be affected by regulation of nicotine levels in both types of products.

The mechanisms underlying non-daily smoking are not fully understood. Early hypotheses proposed that ITS metabolized nicotine more quickly than DS, thereby minimizing nicotine's subjective and physiological effects, or that ITS metabolized nicotine more slowly than DS, resulting in the need for fewer cigarettes to experience the reinforcing and withdrawal-

relieving effects of nicotine. However, recent evidence suggests that the rate of nicotine metabolism does not differ between DS and ITS, but instead, ITS are thought to extract more nicotine *per cigarette* than DS [8]. ITS are also known to smoke more often when away from home or consuming alcohol and socializing [76], suggesting ITS smoke in more "indulgent" or positive situations.

As previously noted, ITS are more likely to try e-cigs than DS [6]. Given the typically low levels of nicotine exposure available from most current e-cigs, the absolute level of nicotine in the e-cig might be less important for ITS than the contrast it creates moving from very low or zero "on-board" levels of nicotine to some potential peak, which would be consistent with the notion of ITS deriving more positive reinforcement from nicotine. This is in contrast to DS, who may be driven to modulate levels of nicotine more or less continuously as a means to forestall withdrawal. Thus, upon regulation of nicotine levels in cigarettes, ITS might compensate for the low nicotine yield of VLNCCs by self-titration using either high or low dose nicotine e-cigs. In fact, ITS might be more likely to switch exclusively to e-cigs rather than dual use with VLNCCs because they are less likely to seek the conditioned reinforcing effects (e.g., sensorimotor stimulation) associated with combustible product use than DS [80], and more likely to maximize the immediate reinforcing experience of nicotine self-administration. Furthermore, ITS might be more amenable to both low- and high-dose e-cigs, given their low frequency of consumption and the corresponding pharmacokinetics allowing for greater extraction of nicotine per cigarette than DS [8]. For DS, on the other hand, the pharmacokinetics of more frequent smoking affords extraction of less nicotine per cigarette [8], which suggests that only high-dose e-cigs will provide sufficient nicotine to achieve "optimum" neural functioning.

Recent links between vaping and lung injury. Beginning in the summer of 2019, a nation-wide outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI) was brought to the attention of the CDC. In terms of EVALI-related fatalities and lung injury, no specific electronic cigarette product has been linked to them, including the products proposed to be used here. In fact, recent (11/7/19) CDC data suggests that this outbreak of lung injury, which began around June 2019, has been experienced primarily by individuals vaping oils containing tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana. The CDC data on 2051 patients with EVALI showed that 86% reported vaping THC oils, that 34% reported using THC oils exclusively (i.e., they did not vape nicotine), and that 11% reported only vaping nicotine products [81]. Many of the samples tested by the FDA and other agencies found evidence of adulterants, including vitamin E acetate [82]. A recent report (11/8/19) by the CDC found vitamin E acetate in the bronchoalveolar lavage fluid of all 29 individuals with EVALI who were tested using isotope dilution mass spectrometry methods [83]. Additionally, as of 10/14/19, 93% of those with EVALI in Texas admitted to vaping THC products [84]. While this does not exonerate nicotine-only vaping, these findings suggest that (a) lung injury due to vaping is due to a product or additive recently added to the market, (b) THC oils, or an additive to these oils, are likely the cause of this recent outbreak of lung injuries, and (c) closed-tank (i.e., resistant to adulteration) nicotine-only electronic cigarette systems, including JUUL, are unlikely to cause adverse events, including those related to lung injury. The CDC appears to be satisfied with this explanation, and discontinued EVALI data collection on 2/25/2020 [85]. As of this writing, we have verified with the manufacturer that none of the current cases of EVALI have involved a JUUL product. Investigation by the CDC is on-going. The concerns specific to the JUUL device have been centered on its rapidly growing popularity among adolescents, to date. However, this protocol will exclude individuals less than 21 years of age, consistent with recent (as of 9/1/2019) changes in Texas law. It is possible that e-cigarettes may cause lung injuries or other serious health problems, which study medical monitor Dr. Karam-Hage and his team will monitor, along with our collaborator from the Department of Pulmonary Medicine, Dr. Ostrin.

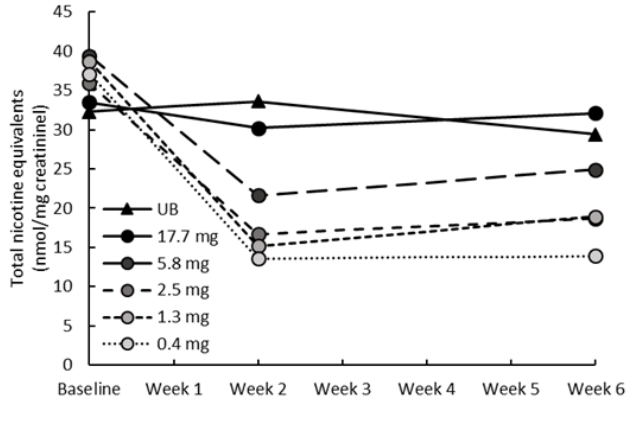
Preliminary Studies

Overview. This project will be led by Drs. Cinciripini and Robinson and carried out entirely at MD Anderson. The investigative team will include Drs. Donny and Hatsukami (VLNCC and nicotine compensation expertise), Eissenberg (e-cig expertise), Murphy (biomarker expertise), and Wetter (EMA expertise).

Identifying the impact of VLNCCs and e-cigs on abuse liability. The assessment of abuse liability involves determining both the likelihood of engagement in the problematic use of a drug, as well as the likelihood of undesirable consequences as a result of this use [86, 87]. The current study will use a multi-level approach to operationalize nicotine abuse liability, including measures of nicotine compensation (TNE, MA, and expired CO), product specific use (CPD; e-cig cartridge weight/puff counter); product specific liking (implicit attitudes, perceived harm, and satisfaction), RRE (purchase task indices) and multi-modal assessments of withdrawal, craving, affect and satisfaction. Co-I Dr. Eissenberg and colleagues conducted an initial abuse liability laboratory assessment of e-cigs, including a multiple choice procedure, a nicotine delivery profile, subjective effects, tobacco abstinence symptom suppression, and product acceptability ratings. Results indicated that although e-cigs delivered clinically significant amounts of nicotine and reduced withdrawal symptoms, they may have a lower potential for abuse relative to traditional tobacco cigarettes [12]. Likewise, in the TCORS projects described in more detail below, Drs. Donny and Hatsukami examined the abuse liability of VLNCCs at multiple nicotine doses, including measures of nicotine compensation, nicotine and toxicant exposure, dependence, and suppression of withdrawal symptoms [9]. To our knowledge, no study has investigated the RRE of usual brand cigarettes versus VLNCCs and e-cigs.

Choice of VLNCC dose. The current study will leverage the results from two TCORS projects which informed our design and the formulation of our hypothesis. The VLNCC nicotine dose for the current study (0.03 mg nicotine/cigarette or 0.4 mg/g tobacco) is based on data (N=839) from our TCORS (U54DA031659; Donny & Hatsukami) [9]. The primary objective of this U54 project is to identify an optimal VLNCC nicotine dose which provides minimal levels of reinforcement and yet remains acceptable to smokers. Non-treatment-seeking smokers participated in a 1-week baseline of usual brand (UB) smoking and were then randomized to smoke VLNCCs, ranging in dose from 0.8 mg nicotine to 0.03 mg nicotine per cigarette (17.7 mg - 0.4 mg nicotine/g tobacco) or usual brand (UB), for the next 6 weeks. The data suggest that relative to the UB group, those in the VLNCC 0.03 mg group smoked fewer cigarettes (-7.58 CPD), and importantly, showed precipitous drop (44%; see **Figure 1**) in TNE. The 0.03 mg nicotine group also showed reduced dependency (FTND, not including CPD in the calculation) and no compensatory increase in CO, nicotine withdrawal, depression, or other adverse events. This latter comparison suggests that, among VLNCCs, 0.03 mg is the best choice for future studies of nicotine reduction, and is the dose selected for remaining U54 projects and the current study.

Figure 1. Total Nicotine Equivalents over time by dose (mg nicotine /g tobacco). UB=Usual Brand; 0.4 mg/g tobacco =0.o3 mg nicotine/cigarette.

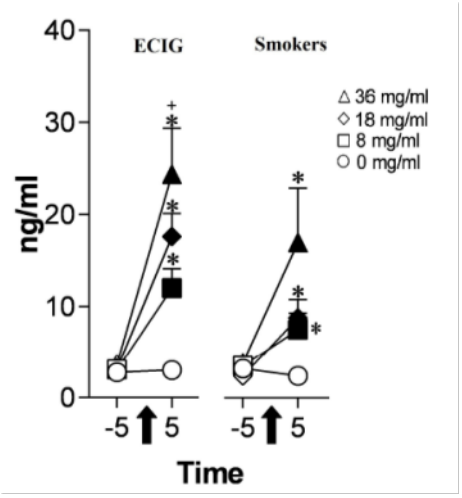


Early e-cigarette configuration and nicotine dose. Co-I Dr. Eissenberg and colleagues have conducted several

clinical laboratory studies investigating the acute effects of e-cig use on abuse liability and withdrawal symptoms [12, 55, 56]. Two of these initial studies suggested that early generation e-cigs may be "insufficient nicotine delivery devices" due to a lack of reliably higher nicotine plasma levels after puffing (10 controlled puffs), though participants reported increased acceptability and reduction in withdrawal symptoms after using e-cigs in the laboratory setting [12, 56]. A subsequent clinical laboratory study reported that e-cigs resulted in reliably increased nicotine levels after 40 puffs, decreased withdrawal symptoms, and higher product acceptability, but was considered less reinforcing than the usual brand cigarettes. The authors concluded that the abuse liability for e-cigs may be lower than normal brand cigarettes but that individuals may need to puff more frequently to experience similar nicotine effects [12].

Choice of e-cig configuration and dose for this study. The e-cig device and dosages in the current trial are based on preliminary studies from another TCORS (P50DA036105; Eissenberg & Balster). In preparation for use in a clinical trial aimed at smoking reduction (Eissenberg & Foulds), Dr. Eissenberg and his team have conducted an extensive analysis of the engineering, aerosol nicotine content (i.e., yield), and plasma nicotine delivery of e-cigs, with the goal of identifying a device/nicotine liquid combination capable of delivering cigarette-like doses of nicotine to humans. This work began with an analysis of the factors that influence the nicotine yield, including battery voltage, nicotine concentration, puff duration, and the resistance of the nicotine cartridge. Based on data from the engineering laboratory and initial experimentation with humans, they have selected the commercially available eGo (Joyetech Co., Shenzen, China), with a 3.5 ml cartomizer, a 3.3 v 1000 mA battery, and dual-coil low resistance (1.5 Ω) cartridge. An ongoing study compares the plasma nicotine concentration of experienced e-cig users and e-cig-naïve cigarette smokers, taking 10 puffs from an e-cig using this configuration, across four independent sessions that differ by the nicotine concentration of the liquid in the cartridge: 0, 8, 18, or 36 mg (all verified beforehand by mass spectrometry). The pre- and post-puffing plasma nicotine concentrations from 11 e-cig users and 13 e-cig naive tobacco cigarette smokers who have completed thus far are shown in **Figure 2.**These preliminary results suggest that plasma nicotine concentrations are related to liquid nicotine concentration in both groups, with 10 puffs from the 36 mg/ml cartridge using the 3.3 v battery delivering a nicotine dose that equals or exceeds that provided by 10 puffs of a conventional cigarette (e.g., >18 ng/ml), while the 8 mg/ml dose does not [56]. Hence for our study, we will use the same hardware and the 36 or 8 mg/ml nicotine solutions (verified by GCMS for the ECIG-Hi and ECIG-Lo conditions, respectively.

Figure 2. Plasma Nicotine By e-cigarette liquid concentration**.**



Experience using smartphone EMA assessments of smoking behavior. Our EMA assessment approach permits examining both acute moments and patterns in momentary data over time (e.g., trajectories) [88, 89] collected in real-time. In addition we also implement a daily diary to provide composite information on the subject's impression of events on the previous day. Our Co-I, Dr. David Wetter, has extensive experience designing and analyzing EMA data to assess smoking behavior and has previously published with PI Cinciripini on this topic. Examples of our previous EMA work include demonstrating that abstainers, early lapsers, and late lapsers exhibit significantly different withdrawal trajectories (i.e., intercepts, slopes, volatility) [88]; that smokers report higher and more volatile craving to smoke on drinking days, and craving to smoke during the day leads to

subsequent drinking [90]; and other studies examining smoking outcome expectancies and mood [91–94].

D. RESEARCH DESIGN AND METHOD

In the current COVID-19 pandemic environment, we will be moving all in-person procedures to a virtual setting, using an institutionally approved platform (e.g., Zoom), until we are able to resume normal operations at our MD Anderson clinic. The following sections have been modified to include the study team's plan for adapting the identified in-person procedures to a virtual setting.

Study overview

Participants will be up to 380 (including up to 80 intermittent [ITS]) non-treatment-seeking adult smokers who are not regular e-cig users. Participants will smoke their usual brand (UB) during Phase 1 (Baseline; week 1) and will exclusively smoke the VLNCC during Phase 2 (weeks 2-4). During phases 3 (weeks 5-7) & 4 (weeks 8-10), smokers will be instructed to freely use any combination of assigned VLNCC and e-cigs (VLNCC+ECIG). All subjects will receive both e-cig doses (ECIG-Hi [36 mg/ml] and ECIG-Lo [8 mg/ml]) with order counter balanced across phases 3 and 4. At least 80 daily smokers will be randomized to the JUUL condition (VLNCC for phase 2 and combined VLNCC+JUUL-Hi or -Lo for phases 3 & 4). All participants in the JUUL group will receive both e-cig doses (JUUL-Hi [JUUL 5%; 59 mg/ml nicotine] and JUUL-Lo [JUUL 3%; 35 mg/ml nicotine]), with order counter-balanced across phases 3 and 4.

Assessment of nicotine abuse liability. We will be measuring abuse liability using multiple domains. In terms of the 5 abuse liability domains described by Carter and colleagues [5], we will be capturing 4, including acute dose-effect comparisons (ECIG-Hi vs. ECIG-Lo), suppression of withdrawal and craving (in-session withdrawal and affect questionnaires; EMA measures of withdrawal, craving, affect), self-administration (RRE; nicotine compensation: TNE, MA, expired CO), and choice procedures (product choice between VLNCC and ECIG during dual use phases). For Aims 1 and 2, we will assess abuse liability in terms of nicotine compensation (i.e., urinary TNE and MA, expired CO) and product use, product liking (i.e., implicit attitudes, perceived harm, satisfaction), and RRE (i.e., purchase task valuation) at the end of each study phase. To assess product use for Aims 1 and 2, participants will be provided with smartphones prior to the start of phase 2 for once daily recording of CPD (also a primary outcome) and e-cigarette use (puff counts from device). For Aim 3, we take a multi-modal approach to the measurement of withdrawal, craving, affect and satisfaction (reinforcement) which provides progressively more sensitive assessments that range from traditional measures (questionnaires filled out weekly) to the smartphone daily diary (patients overall assessment of the day) to real-time measures captured through EMA. Questionnaires will be administered at each of the 5 in-person sessions, smartphone daily diary will be collected during phases 2, 3, and 4, and smartphone EMA assessments will be conducted in phases 3 and 4 only.

COVID-19 adaptation: Enrolled participants will be mailed free study smartphones prior to the start of phase 2 to be used for the duration of their participation in the study.

Participants

We will recruit up to 380 adult smokers (approximately 50% women) from the state of Texas and/or Houston areas. Inclusion and exclusion criteria are listed in Table 3. To facilitate compliance, participants will be compensated for completing visits, smartphone assessments and returning biological samples as described below.

COVID-19 adaptation: While this study is being conducted virtually, we will expand participant recruitment to the state of Texas.

Procedures

Phone screen: Initial eligibility. All participants will be screened by phone (or in-person if a walk-in) to determine initial eligibility (i.e., age, self-reported exclusionary medical/psychiatric conditions and product use criteria). All participants who are initially eligible will be informed that they may be sent an email with a questionnaire consent statement, and, should they consent (by checking "I agree" at the bottom of the statement and typing in their initials), they will be automatically connected to participant specific (i.e. linked to the specific participant) screening questionnaires hosted on MD Anderson's Qualtrics platform, prior to their scheduled baseline laboratory or virtual session. The emailed statement will automatically be sent by our database system up to 5 days before the scheduled appointment. Participants will have up to 5 days prior to their appointment to access the link through their email acknowledge their agreement and complete the questionnaires. Participants will receive a phone call, email, and/or text message before their laboratory or virtual sessions to remind them of the appointment. Eligible participants will be scheduled for an in-person or virtual screening. In addition, as applicable during the SARS-CoV-2 pandemic and recovery phase, MD Anderson institutional COVID-19 screening requirements will be reviewed with the participant and their verbal acknowledgement obtained before scheduling the in-person screening visit.

COVID-19 adaptation: No adaptions needed. The initial eligibility screen is already being conducted remotely over the phone.

In-person screening session. Participants will be instructed to smoke ad libitum prior to this session. They will complete basic demographic, health and smoking history questionnaires used in our previous studies that will be reviewed and approved for eligibility by a licensed medical provider. Tobacco product consumption rates will be established using a timeline follow back procedure [95] and smoking history measures used in previous studies [70]. Psychiatric stability, including suicidality criteria, will be assessed using the PHQ-9 [96], a measure of depressive and suicidality symptoms, and the GAD-7 [97], a measure of anxiety symptoms. We will also assess nicotine dependence (Fagerström Test for Nicotine Dependence; FTND) [98] and expired CO. Any individual who is deemed ineligible for study participation for medical/psychiatric reasons will be referred to local medical and/or psychiatric resources. Any participant who spontaneously reports mood, hopelessness, anxiety and/or other symptoms suggesting a persistent change in mood, or who expresses suicidality, will activate the mental health procedures described in Appendix Z.

COVID-19 adaptation: Eligible participants will be scheduled for a virtual "in-person" screening session using an institutionally approved platform, such as Zoom.

Phase 1: Baseline (week 1). During this phase, participants will be instructed to smoke their usual brand *ad libitum*.

COVID-19 adaptation: No adaptations needed.

Phase 2: VLNCC only (weeks 2-4). During Phase 2, participants will be instructed to smoke only the VLNCCs provided by the study. At the beginning of this phase, they will be given 3 weeks' worth of VLNCCs (150% of their baseline usual brand amount). Regular or menthol will be provided according to their preference. While participants will be asked to use study cigarettes exclusively, they will not be penalized for smoking non-study cigarettes and will be asked to report any such use throughout the study. However, a specific, biochemically verified compensation plan related to VLNCC use will facilitate compliance and honest reporting, as described in the compensation and compliance section below. Smartphone diary assessments as described below will begin during Phase 2. A check-up call may be conducted around 3 days after the start of Phase 2 to troubleshoot any problems the participant may have in terms of starting a new study product. This will allow staff to address any issues that a

participant is experiencing sooner rather than the next scheduled contact, which is approximately 21 days after the visit. Participants are asked to bring all VLNCC products back at each visit whether opened or unopened for purposes of accounting (see Appendix KK).

The VLNCCs are made from genetically engineered tobacco strains that vary in nicotine content and are produced by RTI International (Research Triangle Park, NC), under NIDA contract (NOT-DA-14-004). As noted earlier, the VLNCC dosage, 0.03 mg, was selected from a multisite FDA-sponsored TCORS (U54DA031659 Project 1; PIs: Hatsukami & Donny) designed to identify a dosage that was minimally reinforcing yet acceptable to smokers.

COVID-19 adaptation: Participants will be mailed their 3-week allotment of VLNCCs prior to the start of this phase.

Phases 3 & 4: VLNCC+ECIG (weeks 5-7, 8-10). During Phases 3 & 4, participants will be provided with the same weekly allocation of VLNCCs as in phase 2, as well as a supply of e-cigs. During these phases, participants will be encouraged to freely use any combination of the VLNCCs and their assigned ECIG product, ECIG-Hi or ECIG-Lo, randomized within-subjects by phase (i.e., Phase 3: ECIG-Hi, Phase 4: ECIG-Lo; or Phase 3: ECIG-Lo, Phase 4: ECIG-Hi). Those assigned to the eGo ECIG arm will receive 2 eGo LCD batteries (1100 mA; 3.3V battery) with puff counter and charge level display, 1 e-cig Universal AC-USB Adapter, 1 USB recharger, a 3 week supply (21 days) of 510 XL Dual Coil Cartomizers (1.5 Ω), a user manual, and a carrying pouch at the beginning of phases 3 and 4. The ECIG-Hi and ECIG-Lo cartomizers will contain 1 ml of 36 mg/ml or 8 mg/ml nicotine solution, respectively, in the flavor (tobacco, fruit, cream, or menthol) of each participant's choice.

Participants randomized to the JUUL arm will be provided with the same weekly allocation of VLNCCs as in phase 2, as well as a supply of JUUL e-cigs. During these phases, participants will be encouraged to freely use any combination of the VLNCCs and their assigned JUUL product, JUUL-Hi or JUUL-Lo, randomized within-subjects by phase (i.e., Phase 3: JUUL-Hi, Phase 4: JUUL-Lo; or Phase 3: JUUL-Lo, Phase 4: JUUL-Hi). Each participant will receive JUUL Device Kits (2 rechargeable JUUL devices and 2 USB chargers), a supply of JUULpods to last to the next laboratory session (one pod/day), and a user manual. The JUUL-Hi and JUUL-Lo JUULpod cartomizers will contain 1 ml of 59 mg/ml or 36 mg/ml nicotine solution, respectively, in the flavor (tobacco or menthol) of each participant's choice.

At the beginning Phase 3, participants will receive training in how to use the ECIG product. They will participate in hands-on training that will include e-cig assembly (battery and cartomizer), turning the cartomizer on and off, puffing, and recharging the battery. The training session will include a minimum of three bouts of 10 puffs each in which the user will be encouraged to vary puff topography to maximize desired sensory qualities of product use. Participants will be able to try and choose from tobacco, fruit, cream, or menthol flavored nicotine solutions (see Appendix JJ). This procedure is similar to what is used in the P50 TCORS led by our co-investigator Dr. Eissenberg. A check-up call may be conducted around 3 days after the start of Phase 3 to troubleshoot any problems the participant may have in terms of starting a new study product. Participants are asked to bring all ECIG products back at each applicable visit whether used or unused for purposes of accounting (see Appendix LL).

Participants and study staff will be blind to ECIG nicotine dose condition. The eGo cartomizers will be shipped from the vendor to the study Program Director at MD Anderson and then taken over to Greenpark Pharmacy or will be shipped directly to Greenpark, who will fill them with the appropriate volume, concentration, and flavor of nicotine solution. Senior staff that are unblinded (i.e. do not have direct patient contact) will store and manage the inventory and labeling of blinded products. Study staff will distribute the product to patients at each visit. The nicotine solution will be procured through AVAIL Vapor, LLC and shipped to the study Program

Director at MD Anderson and then taken over to Greenpark Pharmacy or will be shipped directly to Greenpark following quality assessment for nicotine concentration using GCMS. Returned or unused study product will be destroyed per institutional guidelines. Avail Vapor and other comparable vendors will supply the e-liquid for use in the eGo ECIG. We will purchase the JUUL devices and JUULpods from a local retailer.

COVID-19 adaptation: Participants will be mailed their 3-week allotment of study ECIGs and VLNCCs prior to the start of phases 3 and 4 by a study staff member blinded to the nicotine dose.

30 Day Follow up Phone Call Participants will receive a follow-up phone call between ideally 30 and 45 days after the final clinic visit (or scheduled Visit 4 completion date) to assess any open AEs and to complete Timeline Follow-Back since their last visit, however, the end of the window will not close until Timeline Follow-Back is collected or the study ends, whichever is sooner. If the participant became pregnant during the study, this would have been recorded as an adverse event. During this phone call, the research assistant will confirm her due date. This event will remain open until delivery. At that time, the licensed medical professional will contact the participant to ask a few questions about the baby's health and will update the Adverse Event.

COVID-19 adaptation: No adaptions required.

Measures

In-person assessment of product use, smoking behavior, and withdrawal. At each in-person or virtual session, participants will provide a urine sample to measure TNE and MA, and provide expired CO (except at screening, where urine for TNE/MA is not collected because participants are not on study product yet). If the session is conducted virtually, expired CO will not be collected. Research assistants will also complete a Time Line Follow Back (TLFB [99]) interview to record nicotine product use up to 30 days before screening and/or up to and including last contact, including CPD (VLNCC and own brand) and number of e-cig sessions per day. The *primary* measure of CPD will come from the daily diary data. TLFB will be used as a secondary source to supplement missing data. Participants will be required to return used and unused VLNCC packs and e-cig cartomizers at each session for compliance/accounting analysis. Cartomizer weight, before distribution and upon return will provide an estimate of total product use, which will be used in conjunction with the diary data. Participants will also complete a computerized battery of questionnaires, including nicotine withdrawal (Minnesota Nicotine Withdrawal Scale; MNWS [100]), craving (Questionnaire of Smoking Urges-Brief; QSU-Brief [101]) and affect (Positive and Negative Affect Scales; PANAS [102]). Unlike the diary data which is obtained daily, or the EMA assessments that occur in real-time, these questionnaire measures cover broader segments of time (i.e., past 7 days). Missing assessments or items are expected and acceptable and are not considered a protocol deviation/violation.

COVID-19 adaptation: We will ask participants to collect and ship their urine samples to us using postage-paid supplies that we will mail to them. TLFB will be collected virtually by study staff. We will also provide postage-paid shipping supplies for participants to return all used and unused VLNCC packs and e-cig cartomizers or JUUL pods. Questionnaires will continue to be administered electronically via the institutionally-approved web-based Qualtrics platform administered over the study smartphones. However, due to the restrictions in place limiting community and employee access to MD Anderson's campus, we will temporarily waive CO collection. CO collection will resume when MD Anderson has moved to a phase in which community participants are permitted on campus and in the Behavioral Research Treatment Center (BRTC) in the Duncan Building (or at another approved on-campus or offsite location).

In-person assessment of explicit product liking. Self-reported liking will be measured at the end of each phase using Product Evaluation Scales (PES), which are modified versions of the Cigarette Evaluation Scale (CES [103]). The CES is an 11-item questionnaire that evaluates the cigarette smoking experience in terms of satisfaction, good taste, dizziness, ability to calm, concentration, wakefulness, reduction of hunger, nausea, irritability, enjoyment of sensations of smoke, and craving reduction. We will use 3 versions of the PES to evaluate usual brand, VLNCC, and ECIG product liking (see Appendix T). To assess perceived product harm, we will administer modified Perceived Health Risks questionnaires (PHR) that will assess beliefs about the addictiveness and health consequences of own brand, VLNCC, and ECIG products (see Appendix X).

COVID-19 adaptation: No adaptations needed. These questionnaires are currently administered electronically using Qualtrics over study smartphones.

In-person assessment of implicit product liking. At the end of each product exposure phase, participants will complete Implicit Association Tests (IAT) designed to evaluate attitudes towards usual brand, VLNCCs, and ECIGs (see Appendix U). The IAT has been used to evaluate attitudes toward consumer products [104, 105] and is comprised of two tasks. In the first task, participants are instructed to rapidly distinguish between two paired products and attributes (e.g., cigarettes + good vs. e-cigs + bad) using two assigned response buttons. In the second task, the pairings are switched. By calculating a standardized difference score between the reaction time differences, one can determine which products and attributes are more strongly associated in memory, thus determining whether an individual has a relatively more positive or negative attitude toward one product vs. the other [106]. We have substantial previous experience with this task using established methods [107] in our studies. For each of the 3 products of interest, we will create 24 pictures that minimize product branding. The good and bad attribute words will come from a previously published set from our lab [108]. To score the IAT, we use the standardized difference score method recommended by Greenwald and colleagues whereby the standardized difference score (D) between mean response times per trial are computed and divided by the pooled SD [109]. Each IAT product comparison will take approximately 8 minutes to complete.

COVID-19 adaptation: We will adapt the IAT to a web-based platform, and will ask participants to complete the task electronically by accessing a hyperlink using the study smartphone.

In-person assessment of product Relative reinforcing efficacy (RRE) using purchase tasks (PT). At the end of each phase, participants will complete 3 hypothetical PTs (see Appendix V). PTs are behavioral economic reward valuation tasks that have been used to assess the RRE of food [110], alcohol [111], illicit drugs [112], and nicotine products [113]. The PT provides an estimate of how much a participant is willing to pay (i.e., its valuation) for a given product (VLNCC, UB, ECIG) over a range of unit price intervals ($0.01 to $1,000). Responses will be used to compute five demand indices, including breakpoint (first price at which consumption goes to zero, i.e., unwilling to pay), demand intensity (consumption at the lowest price), O_{max} (maximum financial expenditure on the product), P_{max} (price at which expenditure is maximized), and elasticity of demand (sensitivity of product consumption to increases in cost). These relative values will be compared across the different products to determine their RRE.

COVID-19 adaptation: Study staff will administer the purchase tasks during the virtual "in-person" sessions with participants using an institutionally approved platform, such as Zoom.

Smartphone Assessments of Withdrawal, Craving, Affect, Satisfaction, Frequency, and Duration of Product Use. Two categories of smartphone assessments will be implemented. One is a limited daily diary assessment which occurs only once per day, and will

provide measures of product use (CPD; e-cigarette puff count from device), withdrawal, craving, affect and satisfaction (reinforcement). The other is a random EMA assessment that will occur twice a day and will provide real-time measures of these same constructs (see Appendix II). To limit assessment burden, once daily diary assessments will occur in phases 2, 3, & 4, whereas by design, the user initiated and random EMA assessments occur only in phases 3 & 4. In the U54 preliminary study, an interactive voice response system was used to collect daily CPD. Here, we use the smartphone-implemented diary to collect CPD because we believe that it will provide superior reliability, as well as other advantages described below. The random EMA assessments are limited to phases 3 & 4 because our *primary* interest in these assessments is to longitudinally explore withdrawal, craving, affect and satisfaction related to dual product use among DS and ITS, including the differential effects of ECIG dose. EMA while smoking regular cigarettes has been thoroughly studied in DS and ITS by Shiffman and colleagues [70, 71, 73, 75, 76] and need not be replicated here.

Our smart phone assessments are modeled after several of our previous studies in which we enrolled very diverse smoking populations [88, 90, 94]. We will make modifications to accommodate the ITS as outlined by Shiffman [70, 73] and provide training to participants relevant to each assessment type and study phase (see Appendices PP and RR).

The daily diary assessments will occur 30 minutes after waking and will assess 6 measures from the previous day, including CPD (VLNCC/UB), 8 items based on the QSU, PANAS and MMWS to assess withdrawal, craving, affect (negative and positive) and satisfaction. For the random EMA assessments (phases 3 & 4 only), participants will be prompted to complete up to 2 assessments associated with product use (based on smoking rate-see below). To enhance compliance, the smartphone will provide immediate feedback, as described in the compensation section below.

For the random assessments, each day will be divided into 2 blocks. Within each block, 1 EMA assessment will be randomly triggered to assess withdrawal, craving, affect, and reinforcement. The software prevents random assessments from occurring within 15 minutes of other assessments. Because prompts may occur at inconvenient times, participants can choose to not participate in that random assessment.

EMA "booster trainings" are provided at all in-person or virtual visits [114].

Total time devoted to EMA is fairly reasonable (between 10-15 minutes/day on average), with compliance rates observed of >75% in our previous research and that of others [88, 90, 94]. Our previous research has shown EMA reactivity is nonexistent or small [115]. We have extensive experience implementing and developing EMA programs and analyzing EMA data related to smoking behavior and anticipate no issues in carrying out this aspect of our proposal [88, 90, 94, 116, 117].

COVID-19 adaptation: No adaptations needed.

Other Important Smartphone Features. This will include automatic real-time download of data to our secure server, appointment and specimen collection reminders (see biomarkers below), as well as the option to call/ text participants if expected data are not forthcoming (e.g., no diary input on a given day). If reports show no EMA data for at least 2 consecutive days, study staff may contact the participant to troubleshoot.

COVID-19 adaptation: No adaptations needed.

Financial Compensation for Behavioral Assessments. Participants may earn $40 for completing assessments at each in-person or virtual visit; $10/phase for returning home-collected urine samples; $2/instance for completing daily diaries (done only once per day) in

phases 2 – 4; and $3/instance for completing EMA assessments (completed up to 2 times/day) in phases 3 and 4; $10 for completing questionnaires electronically prior to the study visit and $30 for returning their study phone in working order (including the accessories that were issued with the phone like charger, cord, case and screen protector, etc.). Because the total possible compensation is greater than $600, subjects will be asked to complete a W-9. Study staff will inform the appropriate contact in the MD Anderson Treasury Services/Tax Compliance when a subject reaches the $600 threshold and will provide the W-9 for reporting purposes. Subjects will be informed that the study payments are considered taxable income and reportable to the Internal Revenue Service (IRS). A Form 1099 will be sent to the subject if their total payments are $600 or more in a calendar year.

COVID-19 adaptation: No adaptations needed.

Financial Compensation for VLNCC compliance. We know from our U54 that some participants smoked UB cigarettes during the VLNCC condition (~2-3 CPD). However, the effect of non-compliance was negligible, as TNE, our primary measure of nicotine compensation, dropped significantly by week 3 relative to UB smoking (See **Figure 1**). Such would be the case here as well, although in this study we will provide incentives for VLNCC compliance. In our recent unpublished inpatient study, 23 smokers smoked only VLNCC 0.03 mg cigarettes for one week, while 7 others were permitted to "cheat" by allowing them to smoke 1-2 UB cigarettes in addition to the VLNCC's. We determined that a 0.02 nmol/ml cut-off for anatabine (a minor tobacco alkaloid) would identify non-compliance with smoking the 0.03 VLNCC exclusively, by as few as 1-2 UB cigarettes. Anatabine is derived from tobacco and is not affected by e-cig use, whereas TNE is influenced by nicotine from either combustible or non-combustible sources. Thus, anatabine provides an excellent measure of VLNCC compliance. Subjects will be told that compliers (<0.02 nmol anatabine) will receive a $100 bonus in phases 2 (VLNCC) and 3 & 4 (VLNCC+ECIG). Honest reporters of UB above this level will receive a $10 bonus, while those above this level who do not report UB use will receive no bonus.

COVID-19 adaptation: No adaptations needed.

Sample collection and biomarker analyses. A urine sample (TNE and MA) will be obtained at each visit starting at Visit 1. In addition, participants will be asked to collect a urine sample at home twice a week between appointments, which will be collected at their subsequent appointment. This will allow for better assessment of TNE and MA exposure among low frequency smokers. Smartphones will be used to prompt the participant to obtain the sample**.** If the participant fails to bring in any/all samples, a deviation will not be logged. A spot urine collection will be conducted during the visit in the event no samples are returned. Urine samples will be sent to the University of Minnesota for analysis. Samples will be de-identified containing only the subject ID generated by the study database, visit number, code corresponding to type of sample, vial number and date collected (example, 456123-03-2-5 9/1/2018).

COVID-19 adaptation: Participants also will be asked to collect a urine sample at home on or near the day of their virtual "in-person" visits, starting at Visit 1. For ease of remote collection, we will only ask for participants to complete one urine collection on or near the time of their visit. We will provide postage-paid supplies for participants to ship these samples to the study team for proper storage and analysis.

Total Nicotine Equivalents (TNE) is the sum of total nicotine, total cotinine, total 3'-hydroxycotinine and nicotine N-oxide excreted in urine ("total" refers to the analyte and its glucuronide conjugate) comprise 85 to-95% of the nicotine dose received by a tobacco user [118], and is an excellent biomarker of nicotine uptake, directly measuring a high percentage of the nicotine dose. TNE will be analyzed by liquid chromatography-electrospray ionization-

tandem mass spectrometry (LC-ESI-MS/MS) [119, 120]. Use of TNE will enable us to quantify changes in nicotine exposure through each phase of the study and will be *our primary measure of nicotine compensation between baseline and subsequent conditions.*

Minor Tobacco Alkaloids (MA) will be analyzed using the LC-ESI-MS/MS method [121, 122]. While nicotine is accepted as the major addictive compound in tobacco, several other constituents, such as MA (e.g., anabasine, anatabine, and nornicotine), may also play a role, and the potential differences in these compounds as a function of ECIG and VLNCC use is of interest. *MA will allow us to estimate differential use in combustible vs. e-cig use, and anatabine will allow us to determine smoking of VLNCC vs. UB.*

Quality Control Procedures. Multiple urinary aliquots will be prepared, labelled, and frozen. With each set of samples, 2 aliquots are analyzed. If the results from these 2 aliquots do not agree within 10% of the known amount, then that set of samples is reanalyzed. Negative controls are also included with each set analyzed.

Acrolein DNA Adduct. A supplement was originally approved to quantify the formaldehyde DNA adduct N^6-hydroxymethyldeoxyadenosine (N^6-HOMe-dAdo) in leukocyte DNA samples collected using cheek swabs, but this was changed to the acrolein DNA adduct 8R/S-3-(2'-deoxyribos-1'-yl)-5,6,7,8-tetrahydro-8-hydroxypyrimido[1,2-a]purine-10-(3H)-one (γ-OH-Acr-dGuo) after instrumentation problems experienced by our collaborator. Measuring this acrolein DNA adduct would provide us with a measure of carcinogenesis specific to e-cigarettes [123]. It would complement the biomarkers of combustible tobacco and nicotine exposure that are included as part of this original funded R01, including total nicotine equivalents (TNE; the sum of nicotine, cotinine, 3'-hydroxycotinine and their glucuronide) and minor tobacco alkaloids (MA; i.e., anabasine, anatabine, and nornicotine). A cheek swab will be collected at Visits 1, 2, 3, and 4. Saliva samples will be sent to the University of Minnesota for analysis. Samples will be de-identified containing only the subject ID generated by the study database, visit number, code corresponding to type of sample, vial number, and date collected (e.g., 456123-03-2-5 9/1/2018).

COVID-19 adaptation: Participants will be asked to collect a saliva and/or cheek swab sample at home on or near the day of their virtual "in-person" visits 1, 2, 3, and 4. We will provide postage-paid supplies for participants to ship these samples to the study team for proper storage and analysis. Pending approval by MD Anderson's Research COVID Leadership Team (RCLT), community participants who can provide saliva mouthwash and/or cheek swab sample at an approved collection site will be asked to do so within a week of their scheduled virtual "in-person" visits 1, 2, 3, and 4. Approved sites may include University of Texas MD Anderson, University of Texas sister institutions, other universities or hospitals located in Texas, and/or contracted commercial vendors. Until approval is provided we will suspend collection of these samples, but continue all other aspects of the study.

Assessment of respiratory and other symptoms. For safety reasons, we will assess respiratory health at baseline and at the final study visit using a CareFusion Vmax Vyntus PC-based spirometer (Höchberg, Germany) without a bronchodilator trial (including forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], the FEV1/FVC ratio, and peak expiratory flow rate [PEFR]) that will be administered by study staff trained per American Thoracic Society guidelines [124] under the supervision of collaborator Dr. Ostrin from the Department of Pulmonary Medicine. Dr. Ostrin will oversee spirometric interpretation and quality control for the duration of the trial. We will also assess respiratory symptoms at each visit using the American Thoracic Society questionnaire (ATSQ) [125]. The ATSQ is an 8-item questionnaire that assesses symptoms including coughing, wheezing, phlegm production, and shortness of breath. Study Medical Monitor Dr. Karam-Hage will oversee the collection, review,

and attribution of adverse events (AEs) in this study and will consult with Dr. Ostrin on respiratory-related AEs, as needed.

COVID-19 adaptation: Due to the restrictions in place limiting community and employee access to MD Anderson's campus, we will temporarily waive the inclusion/exclusion criteria related to spirometry (willing and able to complete two spirometry sessions; bronchial or respiratory infection in the last 14 days; subject's spirometry FEV1 percentage reading is <50 [severe to very severe obstruction]). Similarly, visit procedures related to spirometry also will be temporarily waived. The spirometry inclusion/exclusion criteria and visit procedures will be reinstituted when MD Anderson has moved to a phase in which community participants are permitted on campus and in the Behavioral Research Treatment Center (BRTC) in the Duncan Building(or in another approved on-campus or offsite location), and spirometry for research purposes has been deemed safe by the institution.

Statistical Approach & Expected Outcomes

General Data Analytic Approach. We will conduct repeated measures analyses (i.e., across time) using generalized linear mixed modeling (GLMM; Proc MIXED, Proc GLIMMIX, and Proc MCMC; SAS 9.4). Continuous and count data will be analyzed using linear and Poisson regression, respectively (Proc GENMOD; SAS v. 9.4). Evaluation of distributional assumptions will use residual plots and, where possible, formal statistical tests. Depending upon statistical technique, we will address violations of assumptions using transformations, robust estimators, stratification, and/or scaling coefficients. For instance, given the characteristically skewed nature of the TNE distribution the analytic plan and power discuss this variable in its log form. Analyses of data with missing values will utilize multiple imputation for cross-sectional analyses (Proc MI and Proc MIANALYZE; SAS v.9.4) [126], while analyses of repeated measures will rely on GLMM to maximize use of existing data. For analyses that require assessment for differential patterns of missing data, we will use Little's Test of MCAR for continuous outcomes and the Park and Lee's approach for discrete outcomes [127, 128]. We will use pattern-mixture modeling methods to address non-ignorable missing data patterns [129]. We will use sensitivity analyses to evaluate the robustness of findings to missing data assumptions. Finally, the False Discovery Rate approach will be used to correct for multiple testing [130].

Aim 1: To characterize the effects of switching to VLNCCs plus ECIG-Hi or ECIG-Lo nicotine doses on abuse liability among daily and intermittent smokers. *Our primary measures of abuse liability will be CPD (product use) and nicotine equvalent (TNE) levels (nicotine compensation). We hypothesize that compared with the VLNC+ECIG-Lo phase, smokers will show decreased CPD and TNE levels during the VLNC+ECIG-Hi phase*. To address these hypotheses, we will use GLMM to evaluate the effects of ECIG dose on measures of nicotine abuse liability, including cigarettes per day and TNE levels.

Aim 2 (Exploratory): To explore the effects of switching to VLNCCs plus ECIG-Hi or ECIG-Lo nicotine doses on abuse liability using biochemical measures of product use, compensation, and toxicant exposure, and self-reported measures of withdrawal, craving, affect, and satisfaction. *On an exploratory basis, we will examine the differences of ECIG dose (VLNC+ECIG-Lo vs. VLNC+ECIG-Hi) on additional measures of abuse liability, including ECIG puff count, withdrawal, craving, negative affect, minor tobacco alkaloid (MA) levels, acrolein DNA adduct levels, expired CO, RRE (i.e., purchase tasks), and liking (implicit attitudes, perceived harm, product satisfaction ratings)*. To address this exploratory aim, we will first use GLMM to evaluate the effects of ECIG dose on the retrospective questionnaire (weekly MNWS, PANAS, QSU) and daily diary (i.e., ecological momentary assessment [EMA]) measures of ECIG puff counts, withdrawal craving affect and satisfaction. To analyze the EMA data of these same constructs, we will use generalized time-varying effect modeling (TVEM)

[131, 132], using the TVEM SAS Macro [133], to evaluate the functional form of these measures of abuse liability over time between high and low ECIG conditions and between ITS and DS groups. These models fit a generalized mixed model with a spline function for characterizing changing abuse liability for the within-subjects conditions (using randomized counterbalancing to address order effects) [134, 135]. Moreover, GLMM will evaluate volatility, as defined by defined by Cofta-Woerpel and colleagues [88], as a function of ECIG dose. Conservatively assuming 15% attrition, 75% compliance and a minimum of five daily EMA measures, each 3-week ECIG dose period should provide n= 5355 observations for each group of ITS and DS smokers respectively. As such, TVEM analyses of EMA-sampled data should have sufficient power for these analyses. We will also use GLMM to evaluate the effects of ECIG dose on measures of minor tobacco alkaloid (MA) levels, acrolein DNA adduct levels, expired CO levels, RRE (i.e., purchase tasks), and liking (implicit attitudes, perceived harm, product satisfaction ratings).

Aim 3 (exploratory): To explore the effects of switching from usual-brand cigarettes to VLNCCs, and from VLNCCs to VLNCC+ECIGs on measures of abuse liability*. On an exploratory basis, we will examine potential changes in the abuse liability measures from Aims 1 & 2 between the UB cigarette and VLNCC only phases, and between those phases and the dual-use phases (VLNC+ECIG-Lo and VLNC+ECIG-Hi)*. We will use GLMM to evaluate the study phase (UB cigarettes, VLNCCs, VLNC+ECIG-Lo, VLNC+ECIG-Hi) and the measures of abuse liability from Aims 1 & 2 to characterize the impact of transitioning between study nicotine products over time.

Aim 4 (exploratory): To characterize the effects of dual use of VLNCC and JUUL ECIGs on abuse liability. *On an exploratory basis, we will examine the differences in measures of abuse liability between the two phases of dual-use (VLNC+JUUL-Lo vs. VLNC+JUUL-Hi) among participants assigned to the JUUL ECIG arm*. We will use GLMM to evaluate the effects of JUUL dose on measures of nicotine abuse liability, including patterns of product use (UB and VLNCC CPD, ECIG puff count), nicotine compensation (TNE, MA, expired CO), product liking (IAT, Product Evaluation Scales, perceived harm, PHR), RRE (Purchase Task indices).

Power analysis. Sample size determination for the current proposal focuses on our primary outcomes for the Aim 1 hypothesis. Effect size estimates are based on our U54 data using the usual brand baseline and 0.03 mg VLNCC conditions to estimate CPD and TNE from those two conditions, respectively [9]. There is no extant data to draw upon for VLNCC+ECIG-Hi or ECIG-Lo conditions for either DS or ITS. Hence, we attempted to estimate the means and standard deviations for CPD and TNE for these two conditions using data from the U54, using the entire sample for DS, and for ITS, limiting the sample to participants in the lowest centile of baseline CPD (<7.3 cigarettes per day). These presumptive means and standard deviations are provided in **Table 1**. While these estimates are not exact they provide a reasonable estimate of the behavior of two groups that vary significantly in their CPD

Table 1. Anticipated effects for DS and ITS, by Phase and E-Cig group.

Primary Outcome	Phase 1: Usual Brand	Phase 2: VLNC Only	Phase 3: VLNC + ECIGs-HI	Phase 4: VLNC + ECIGs-LO
DS				
CPD	19.62 (10.18)	14.19 (10.09)[a]	12.80 (10.00)[b]	12.80 (10.00)[b]
TNE	63.01 (55.87)	33.54 (34.84)	59.50 (53.88)	33.08 (31.27)
log(TNE)	3.89 (0.99)	2.69 (1.65)[a]	3.60 (1.28)[c]	2.72 (1.62)[b]
ITS				
CPD	3.42 (3.44)	2.47 (3.44)[a]	1.57 (3.44)[c]	1.57 (3.44)[c]
TNE	32.5 (17.53)	10 (9.36)	28.37 (22.24)	15.88 (11.16)
log(TNE)	3.31 (0.67)	1.74 (1.49)[a]	3.07 (0.80)[c]	2.31 (1.29)[c]

Primary outcomes are for nicotine compensation (TNE) and CPD. **a**-Significant change between Phase 1 & 2 expected; **b**-No significant change from Phase 2 to 3 expected; **c**-Significant change from Phase 2 to 3 expected.

Table 2. Power Estimates.

Contrast	Anticipated Effect Sizes		Power		Minimum Detectable Effect Size	
DS	CPD (R.R.*)	Log(TNE) (d_z**)	CPD	Log(TNE)	CPD R.R. (Power)	Log(TNE) d_z (Power)
Within Group						
Brand v. VLNC	0.72	-0.78	≥ 99%	≥ 99%	0.89 (83%)	-0.39 (82%)
VLNC v. VLNC-ECIG-HI	0.90	0.56	61.4% x	≥ 99%	0.88 (82%)	0.35 (81%)
VLNC v. VLNC-ECIG-LO	0.90	0.02	61.4% x	5% x	0.88 (82%)	0.36 (82%)
VLNC-ECIG-HI v. VLNC-ECIG-LO	1.00	-0.55	5% x	≥ 99%	1.13 (81%)	-0.35 (80%)
ITS						
Within Group						
Brand v. VLNC	0.72	-1.15	93.9%	≥ 99%	0.76 (82%)	-0.35 (81%)
VLNC v. VLNC-ECIG-HI	0.64	0.96	98.7%	≥ 99%	0.73 (80%)	0.35 (83%)
VLNC v. VLNC-ECIG-LO	0.64	0.37	98.7%	85.7%	0.73 (80%)	0.35 (80%)
VLNC-ECIG-HI v. VLNC-ECIG-LO	1.00	-0.63	5%x	≥ 99%	1.40 (82%)	-0.35 (82%)

*Risk Ratio. ** Standardized effect size accounting for correlation. x No change expected.

and variation in their behavior when exposed to conditions of relatively more (Usual Brand) vs. less (0.03 mg) nicotine availability. Power estimates are based on Monte Carlo simulation or calculations using G*Power 3.0 [136]. We anticipate enrollment of up to 380 participants (including at least 80 ITS). Assuming 15% loss to attrition (in our U54 the completion rate across visits ranged from 92%-100%), we based our power analysis on n = 67 DS and n = 67 ITS.

Table 2 provides power estimates for respective contrasts. For within-group effects the overall posited correlation between adjacent phases was 0.4. Each power estimate was derived from K = 1000 Monte Carlo simulations. **Table 2** summarizes minimally detectable effects, given the anticipated sample size, alpha = 0.05, and the correlations due to repeated measures. **Table 2** also includes minimum detectable effects and corresponding power for each contrast. Minimum detectable effects for CPD (i.e., 80-83% Power) range for Risk Ratios indicating 11% to 40% relative changes for within-group contrasts. Absolute values for standardized effect sizes that constitute minimum detectable effects for log(TNE) (i.e., 80% Power) range from absolute values of d_z = 0.35 to 0.39 for within-group contrasts. While we do not anticipate significant changes in CPD from Phases 2 to Phase 3 or 4 among DS participants, the study will be powered to detect a risk ratio for CPD of 0.88 for VLNC vs. ECIG-HI or ECIG-LO, and a risk ratio of 1.13 for the difference in CPD between VLNC + ECIG-HI and VLNC + ECIG-LO. Similarly, among DS participants we do not anticipate a change in log(TNE) moving from VLNCC to VLNCC-ECIG-LO, however the sample will provide power to detect a standardized effect size of $d_z \geq 0.36$. Among ITS participants, we do not anticipate differences between VLNC + ECIG-HI and VLNC + ECIG-LO in CPD but the sample will provide power to detect a risk ratio of 1.40 if an effect does occur. Power estimates for the exploratory Aims 2, 3, and 4 analyses focuses on the GLMMs for self-report and volatility measures; TVEM approaches will have many more observations than either of these, however fitting the functional form of change over time, and therefore its final parameterization will be largely data-dependent. Assuming alpha = 0.05 and a correlation of r = 0.5 for repeated measures, a sample of n = 67 DS participants provides 80% power for the GLMM to detect a Cohen's f = 0.17. The Aim 4 hypotheses are considered exploratory and were not subject to power analyses, but we should have adequate statistical power to detect the hypothesized differences because it will use the same sample size, design, and outcome measures as Aims 1 & 2.

Potential Problems & Alternative Strategies

Safety of VLNC cigarette and ECIG products. The main addictive substance in tobacco is nicotine. Medicinal nicotine products, such as the nicotine patch, gum, and lozenge, as well as a nicotine receptor agonist (varenicline), are all considered the standard of care for smoking cessation [137] and are prescribed to most patients in MD Anderson's Tobacco Treatment Clinic. Providing nicotine replacement is the primary means to alleviating withdrawal and craving, modulating mood, and make it easier for smokers to quit. In terms of non-medicinal nicotine, we have had four MD Anderson IRB-approved protocols where we provided non-medicinal nicotine to study participants, all of which were NIH-funded and monitored by the FDA. In two of our multisite protocols (U54DA031659), 2012-0039 (n=840) and 2014-0510 (n=1250), we provided study participants with NIDA's very low nicotine content (VLNC) research cigarettes for 6 weeks and 5 months, respectively. The purpose of the first study was to evaluate the feasibility and safety of smoking cigarettes with lower nicotine content, while the second study evaluated implementing a gradual vs. immediate reduction in nicotine content. The FDA has suggested that "weaning" smokers off of harmful combustible cigarettes, while promoting less harmful products such as electronic cigarettes, are policies that they are considering [138]. The main outcomes of these first two studies were published in the New England Journal of Medicine [9] and JAMA [139]. The first study demonstrated that smokers would tolerate and use cigarettes containing nicotine as low as 3% of what is found in a typical cigarette, and the second study showed that switching to this VLNC cigarette can be safely done so either gradually or immediately.

Given the concerns around ECIGS, we have conducted an unplanned interim analysis of the adverse events for this protocol. Thus far, we have exposed 176 adult smokers to NIDA's VLNC combustible cigarette for up to 9 weeks and to commercially available closed-tank electronic cigarettes for up to 6 weeks (the same product being used in many other studies across the country). In terms of adverse events, similar proportions of participants have reported adverse events during the exclusive cigarette phases (18.0%) than during the phase where they are encourage to use electronic cigarettes instead of smoking (15.3%). The most frequently reported adverse events during the electronic cigarette phases included depressive symptoms (n=4), sore throat (n=3), diarrhea (n=2), toothache (n=2), and vomiting (n=2). For the exclusive cigarettes phases, the most common adverse events included cough (n=6), irritability (n=5), headache (n=4), back pain (n=2), diarrhea (n=2), limb edema (n=2), insect bite (n=2), nausea (n=2), panic attack (n=2), and urinary tract infection (n=2). No severe adverse event was reported during the electronic cigarette phases, but one was reported during the exclusive cigarette phases, brachycardia (n=1). None of these were determined to be of probable or definitive relation to the device. No serious respiratory symptoms have been reported. Our retention rate through the end of study has been 77%. The preliminary findings suggest that closed-tank electronic cigarettes are not associated with more adverse events than smoking combustible cigarettes.

While this study is designed as a short term experiment, vaping may have long-term side effects that may not be fully known for another decade or two, as was the case initially for combustible cigarette smoking [140]. However, this is all the more reason to study electronic cigarette products, particularly JUUL, the most popular product on the U.S. market. Data from preliminary studies suggest that electronic cigarettes may be relatively safe out to 2 years of exposure among adult cigarette smokers. A study that switched 209 combustible cigarette smokers to electronic cigarettes and followed them for 2 years found that adverse events probably related to electronic cigarettes were experienced by less than 6% of participants, and decreased over time, and none of the 7 SAEs were judged to be related to study product [141]. In terms of short-term exposure, switching to electronic cigarettes results in significant reductions in exposure to numerous toxicants and carcinogens (e.g., NNAL, CEMA, HEMA, 8-

EPI) compared to smoking combustible cigarettes (see [142] for review). Compared to other electronic cigarette products, the JUUL device has several advantages and safety features, including a limit of heating the vapor up to 300 F, and has been found to emit less toxicants. As we mention in the "Safety of the high nicotine dose ECIG" section, independent studies suggest that JUUL ECIGs produce lower levels of free radicals and carbonyls [143], formaldehyde and total aldehyde yields [144], and benzene [145] than other ECIGs, and much lower levels than combustible cigarettes. These initial findings suggest that while certainly not risk-free, electronic cigarettes are likely to be safter than combustible cigarettes over the long term.

Lack of a cessation endpoint. If we could, we would be submitting protocols to evaluate electronic cigarettes as a potential smoking cessation aid, because anecdotal evidence suggests that smokers are already doing so. Unfortunately, we are not yet able to evaluate electronic cigarettes as a smoking cessation therapy in the U.S. Smoking cessation is considered a medical indication and products making a medical claim are overseen by CDER, which is a separate and independent component of the FDA from CTP, which oversees tobacco and nicotine regulation. Unlike the pharmaceutical industry, no electronic cigarette manufacturers have taken the necessary steps to assemble a master file needed for obtaining an investigational new drug (IND) application, which must be granted before cessation with electronic cigarettes could be studied. Researchers in the US have been complaining about this conundrum for years but it is not something we can control and in fact we cannot have cessation as an endpoint in any of our studies (except for naturalistic quitting). Moreover, because the focus is on harm reduction, we only select smokers who are not presently interested in quitting for our electronic cigarette studies for ethical reasons.

Duration of product exposure. While a one week usual brand smoking is typical for establishing a base rate in most observational studies, the length of the VLNC and each VLNCC+ECIG dose condition (3 weeks each) could be insufficient to determine stable responding. However, in our preliminary studies we observed little change in CPD for VLNCCs beyond week 3. There is no data to estimate length of exposure to e-cigs needed to establish stable responding, but we feel 3 weeks is sufficient since individuals in the high dose condition will receive levels of plasma nicotine comparable to combustible cigarettes within as little as 10 puffs, and this will provide the intended contrast to the lower plasma nicotine levels of the low dose e-cig within the same time frame.

Another potential issue is that the length of the phases may be insufficient to sample ITS smoking behavior. However, Shiffman and colleagues, who have done the most sophisticated work with this population, have used a 21-day (3 week) sample in EMA studies [73]. Additionally, it may be difficult to estimate the "typical" TNE and MA among ITS given their low frequency of smoking. To address this, we collect urine samples twice per week (in Phases 2, 3, and 4) to better estimate these compounds among ITS, and like Shiffman and colleagues [8], we will select for analysis the sample that most closely corresponds in time to smoking their median CPD from Phase 1. If the participant fails to bring in any/all samples, a deviation will not be logged. A spot urine collection will be conducted during the visit in the event no samples are returned.

Finally, rather than conduct random EMA assessments for the entire duration of the study, which would quite burdensome to participants, we have elected to conduct daily diary assessments (once per day) in phases 2-4 and to implement random (up to 2 times per day) assessments only in phases 3 & 4. We feel this is a reasonable trade off to reduce participant burden since our primary interest in the EMA data pertains to the assessment of frequency and circumstances surrounding dual product use. In addition, EMA information during regular smoking has been thoroughly explored for DS and ITS by Shiffman and colleagues [70, 71, 73, 75, 76].

Nonrandom ECIG flavor assignment. By allowing participants to choose a preferred flavor, we will be unable to determine the influence of this factor on our dependent measures in a prospective manner. At most, we will be able to determine the influence of ECIG flavor on our outcome measures in an exploratory fashion (e.g., post hoc sub-group analyses). However, we chose this design to maximize the likelihood that participants will actually use the study ECIG devices during the product exposure period. Recent studies suggest that most ECIG users (over 65%) prefer some type of flavoring, usually a sweet flavor [146]. Moreover, many menthol users specifically eschew any use of nonmenthol products, and thus may find nonmenthol ECIG flavors unpleasant. Thus, in order to sustain ECIG use, we believe it is more important to propose a design that accommodates participant product preference, rather than expose them to a flavor they wouldn't use. We are aware that the FDA is considering a complete or partial flavoring ECIG ban [147]. If such a ban were to occur at a federal (or state) level, we would comply by only offering participants flavor choices allowed by law, which is likely to be tobacco- and possibly menthol-flavored [148] products.

Safety of the high nicotine dose ECIG. JUUL ECIGs currently comprise over 75% of the U.S. market [2] and have some of the highest nicotine concentrations among ECIG products. Safety studies regarding JUUL ECIGs are relatively few, owing to the newness of the product, but these initial studies suggest that the 5% solution (~59 mg/ml of nicotine) produce blood nicotine values and pharmacokinetic profiles comparable to those of combustible cigarettes, but with less toxicants. For example, studies sponsored by JUUL Labs, Inc., have found that JUUL ECIGs produce nicotine pharmacokinetic profiles in adults similar to that of combustible cigarettes [149], with lower levels of toxicants, including volatile organic compounds, polycyclic aromatic hydrocarbon, carbonyls, and ammonia compared to combustibles [150]. In terms of independent verification of JUUL ECIG's nicotine content, one study of adolescent and young adults found that JUUL ECIGs product cotinine levels, the major metabolite of nicotine, similar to those of combustible cigarettes [151]. Another recent study by independent researchers found that JUUL ECIGs produced saliva cotinine levels that the authors noted were comparable to their previous evaluations of lower-dose ECIGs and combustible cigarettes among adults [152]. In terms of toxicants, independent studies suggest that JUUL ECIGs produce lower levels of free radicals and carbonyls [143], formaldehyde and total aldehyde yields [144], and benzene [145] than other ECIGs, and much lower levels than combustible cigarettes. Thus, preliminary data from both independent and industry-sponsored labs suggest that the high-dose JUUL ECIG product produces comparable blood levels of nicotine, and lower levels of toxicants, than combustible cigarettes among adults.

Using a high nicotine dose ECIG such as JUUL may increase nicotine dependence. However, it should be noted that smokers titrate their nicotine level all through the day to maintain the level they are accustomed to, given nicotine's short half-life [153]. In studies of the topography of smoking where smokers are provided with nicotine patches, they automatically smoke less of each cigarette and inhale less deeply [154]. A similar nicotine self-titration appears to occur among electronic cigarette users in studies conducted over 12 [155] and 24 months [156] of product exposure. While it is possible that some smokers who use the JUUL device may experience an increase in nicotine levels and possibly dependence, which we mention in the "Adverse experiences associated with electronic cigarettes" paragraph of the Protection of Human Subjects section, there is no evidence to date to show that dual product users are any more nicotine dependent than exclusive users of combustible cigarettes. We also describe that we will offer all participants 8 weeks of free smoking cessation treatment, including nicotine replacement therapy and smoking cessation counseling, at the end of their study participation, if they wish to do so. This treatment will be provided by MD Anderson's Tobacco Treatment Program under the guidance of Dr. Maher Karam-Hage, the medical director of that program and medical monitor of this protocol.

Future directions. At the project's conclusion we will have identified the extent to which DS and ITS compensate for a loss in available nicotine while using VLNCCs, by using e-cigs that provide varying levels of plasma nicotine delivery. We will also identify factors that influence dual use of VLNCC and e-cigs, toxicant exposure as well as product liking and reinforcement. We will use this data to pursue future studies examining the potential for e-cigs to serve as a cessation aid for those interested in quitting as well as a vehicle for harm reduction among those that do not.

E. PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics and Design

Volunteers recruited for this study (N= up to 380) will be current smokers from the state of Texas area and/or Houston metropolitan community, who respond to media announcements related to the study (see Appendix AA). The Tobacco Research and Treatment Program's web screener database for tobacco users, outlined in IRB-approved PA18-0423, also may be used as a recruitment source for this study. This database houses data collected from an internet-based screening questionnaire to recruit tobacco users from the Houston area, as well as across Texas more broadly, who may be interested in participating in tobacco use and cessation studies at MD Anderson Cancer Center. PA18-0423 allows the sharing of data with IRB approved MD Anderson protocols.The Houston population is estimated at over 4 million with an ethnic distribution of 59% Caucasian, 19% African-American, 5% Asian, and 0.4% Native American, with 33% Hispanic or Latino (of any race) [157].

As shown in **Table 3**, inclusion criteria will include signing consent and agreeing to all study procedures, being between the ages of 21 and 65, having a working telephone and address where they may be reached, being interested in trying novel nicotine products, able to follow verbal and written instructions in English, and be the only participant in their household. Individuals will be excluded if they are unwilling to refrain from other e-cigarette use for the duration of the study, other than what is provided to them for study purposes, have had a bronchial or respiratory infection within the past 14 days, a spirometry FEV1 percentage reading is <50 (severe to very severe), have unstable medical conditions as determined by the medical team, abnormal heart rhythms or cardiovascular disease (stroke, chest pain, heart attack) in the last 3 months, meets criteria for Major Depressive Syndrome or suicidality on the PHQ-9 , self-report of past or current diagnosis of bipolar disorder or schizophrenia/schizoaffective disorder, report use of tobacco products other than cigarettes or little cigars on 10 or more days in the last month, report recent (past 90 days), current, or planned (within the next 45 days) involvement in smoking cessation activities, or have a positive urine pregnancy test at screening.

Women who are one-year post-menopausal, or who have had a tubal ligation or a partial or full hysterectomy will not be subject to a urine pregnancy test. Also excluded are women who are pregnant, breastfeeding or of childbearing potential and not protected by a medically acceptable, effective method of birth control while enrolled in the study. Medically acceptable contraceptives include: (1) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (2) barrier methods (such as condom or diaphragm) used with a spermicide, or (3) an intrauterine device (IUD). Contraceptives sold for emergency use after unprotected sex are not acceptable methods for routine use. Also excluded are participants considered by the investigator to be unsuitable to participate in the study (e.g., due to cognitive deficits or instability to last the entire duration of the study). Daily smokers must report smoking 1 or more cigarettes per day (CPD). Intermittent smokers must report smoking 4 to 27 days per month, but will not be required to meet any minimum for CPD or expired CO, following the practice of Shiffman and colleagues [8].

Table 3: Inclusion Exclusion Criteria.

Inclusion Criteria:
- Sign consent and agree to all study procedures
-Age: 21-65 years old
- Have an address where he/she can receive mail
- Have a device available to conduct telehealth visit (e.g., smartphone, computer, tablet, internet access etc.) - Able to follow verbal and written instructions in English
- Willing and able to complete two spirometry sessions (this criterion waived during COVID-19 pandemic)
-Be the only participant in their household
-Interested in trying novel nicotine products
-Daily Smokers: ≥ 1 cigarette/little cigar per day
-Intermittent Smokers: ≥ 1 cigarette/little cigar per day 4 to 27 days per month
-Agrees to comply with all MD Anderson institutional policies related to COVID-19 screening prior to each in-person research visit.
-The individual agrees to not engage in study procedures or interactions with study personnel while operating a vehicle.

Exclusion Criteria:
-Unwilling to refrain from other e-cigarette use for the duration of the study, other than what is provided to them for study purposes.
-Current/recent use of certain medications:
a. Smoking cessation meds (past 90 days; e.g., Wellbutrin, Bupropion, Zyban, NRT, Chantix)
b. Certain medications to treat depression (last 14 days; e.g., Amitriptyline)
c. A case by case determination will be made by study physician for medication on the precautionary list (e.g., nitroglycerin)
d. self-reported daily use of opioids for 30 days or more on phone screen or at screening is exclusionary however PRN use is allowed (e.g., 3 to 7 days per week or less or if more frequent, use less than a month's duration.)
-Unstable medical condition as determined by the medical team
-Self-reported bronchial or respiratory infection in the last 14 days (this criterion waived during COVID-19 pandemic)
-Subject's spirometry FEV1 percentage reading is <50 (severe to very severe obstruction) (this criterion waived during COVID-19 pandemic)
-Self-reported abnormal heart rhythms or cardiovascular disease (stroke, chest pain, heart attack) in the last 3 months
- Meets criteria for Major Depressive Syndrome or suicidality on the PHQ-9
-Self report of past or current diagnosis of bi-polar disorder or schizophrenia/ schizoaffective disorder
-Self-reported other tobacco use besides cigarettes or little cigars (e.g., hookah, cigarillos, smokeless tobacco, chewing tobacco, pipes, cigars, etc.) on 10 or more days in the last month.
-Recent (past 90 days), current, or planned (within the next 45 days) involvement in smoking cessation activities
-Positive urine pregnancy test at screening. Women who are one year post-menopausal, or who have had a tubal ligation or a partial or full hysterectomy will not be subject to a urine pregnancy test.
-Women that are breastfeeding or of childbearing potential and not protected by a medically acceptable, effective method of birth control while enrolled in the study. Medically acceptable contraceptives include: (1) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (2) barrier methods (such as condom or diaphragm) used with a spermicide, or (3) an intrauterine device (IUD). Contraceptives sold for emergency use after unprotected sex are not acceptable methods for routine use
-Subject considered by the investigator to be unsuitable to participate in the study (e.g., due to cognitive deficits or instability).

Note: For the purpose of eligibility requirements and ongoing smoking status, "cigarettes" will also include the tobacco product that is commonly known as "little cigars". Little cigars are machine-manufactured and sold in packs similar to cigarettes. They are often smoked by individuals of limited means because they are cheaper than conventional cigarettes.

All smokers will be prescreened by telephone for basic eligibility requirements (see Appendices P & CC). An initial description of the study design will be provided and data will be obtained on age, smoking history, other tobacco use, medical and psychiatric history, medication use, and pregnancy/lactation status. All participants who are initially eligible will be informed that they may be sent an email with a currently approved informed consent document for their review, an information slideshow (see Appendix BB.), and a questionnaire consent statement, and that, should they consent, they will be automatically connected to questionnaires hosted on MD Anderson's Qualtrics platform, prior to their scheduled baseline laboratory session. Participants will receive a phone call, email, and/or text message before their laboratory sessions to remind them of the appointment. Eligible participants will be scheduled for an in-person screening and may be emailed or mailed a confirmation letter and parking directions (see Appendix G). Given the nature of the study design it will be necessary to eliminate subjects who do not speak English or have a telephone.

COVID-19 adaptation: Spirometry-related inclusion and exclusion criteria will be waived until normal in-clinic operations are resumed and research-related spirometry is deemed safe to perform by the institution. Participants able to become pregnant will be mailed and asked to complete a pregnancy test at the virtual baseline screening and at Phases 1-4. Participants will be provided instructions for conducting the pregnancy test(s) at home (see Appendix AAA). Participants also will be asked to take a picture of the tests' results and to electronically send the picture to study staff through text or email.

Informed Consent. At the baseline session, the study purpose, other study requirements, and side effects will be reviewed including information related to the study's certificate of confidentiality (see Appendix OO). The information presented may come in the form of a slideshow (either paper or electronic) which will be developed in collaboration with the PI or Co-PI and will be based in part on current studies using VLNCC and/or directly from the informed consent document itself. Participants will be given the opportunity to ask questions about the informed consent document or any aspect of the study. Any medical questions that arise during the

process, if not addressed in the documentation or discussion provided, will be referred to the medical staff and the information will be provided to the potential participant prior to consenting.

Prior to beginning any study related procedures, the participant will review the informed consent document with a trained staff member. During the informed consent process, the participant will be presented with an optional procedure regarding their electronic communication preference (i.e. receiving communication via an unsecured method such as text, unencrypted email, etc. or via secured method such as in-person consultation, encrypted email, telephone calls, etc.). The consenting staff member will review any questions the patient may have, and confirm that they understand the nature of the research being performed.

COVID-19 adaptation: Study staff will review the ICD as detailed above with participants during a virtual “in-person” session, and the ICD will be signed electronically by the participant using an institutionally approved platform.

Sources of Materials. Participants will be providing physiological data in the form of saliva and urine (TNE and MA), expired CO, and vitals. Questionnaire data will be obtained that assess previous smoking, smoking cessation history (including Rx medications and NRT’s), current and past health and psychiatric conditions, mood, nicotine withdrawal, craving, and cigarettes smoked. All data will be collected specifically for research purposes and will be coded to maintain confidentiality. Relevant medical screening data will be shared with the participant as appropriate for referral and follow-up medical care (see Appendix SS).

Baseline Screening.

Participants will not be randomized into the study until Visit 1. Participants who remain eligible after the baseline screening visit will be scheduled to return for Phase 1 as soon as the following week after the baseline visit. Participants will be registered in the institutional database (CORe) within 2 business days of signing consent.

At the baseline screening (Visit 0), which will occur within 30 days of the telephone screen, study participants will be asked to provide medical/surgical history (see Appendices E & QQ), smoking history (see Appendix H) and to complete other assessments as shown in Table 4. Additionally, participants will be asked to fill out two forms related to additional contacts should we no longer be able to reach them (see Appendix C). They may also be provided a staff contacts list and an appointment card if eligible during the visit (see Appendices L and NN). Current and past medical history will be collected. These items will be given to a licensed medical professional, such as a research nurse, physician’s assistant, or MD, to review eligibility. In some cases, the medical team may request clearance for participation be signed off by the participant’s medical provider (see Appendix TT) prior to enrollment.

Participants unable to complete the Baseline screening visit within 30 days of the initial telephone assessment will be allowed to undergo a second telephone assessment and given an additional 30 days to complete the Baseline screening visit. If they do not complete the Baseline by this time point, they will no longer be considered eligible for study participation and must undergo a 90-day waiting period to re-enroll.

Subject Withdrawal

A withdrawal occurs when an enrolled subject actively withdraws consent for further participation in the study, prior to completion of the protocol. Subjects may withdraw consent from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety reasons. All attempts will be made to collect medications, and to conduct all evaluations required by the protocol.

Return Visit Schedule and the Visit Window

A window will be permissible for all return visits as follows. Ideally, visits 1 to 4 will observe a 7 day window. If the end of the visit window falls on a weekend, holiday, or other day on which the clinic is officially closed, subjects will be allowed to complete the visit during the next business day. If a participant is not able to complete a visit in the preferred window, a maximum window of 1 month between phases will be observed but no deviation will be logged for out of window visits as these are to be expected. A No Show letter may be sent in some cases (see Appendix J). Checkup calls will be conducted around 3 days post Visit 1 and Visit 2 and will have a window of 1 business day. If the call falls on a weekend, holiday, or other day on which the clinic is officially closed, participants will be contacted the next business day. The 30 Day Follow up call will take place ideally between 30 and 45 days after the final clinic visit (or scheduled Visit 4 date), however the end of the window will not close until TLFB data is collected, or the study ends, whichever is sooner. Occasionally, participants ask for a Doctor's Excuse or a Travel Letter, which we may provide at our discretion (see Appendices K and M).

Assessments and Questionnaires

A study timeline and table of events and assessments are detailed in **Table 4**. Participants that have agreed to electronically receive questionnaires in advance of the visits will automatically be sent an email containing a participant specific link up to 5 days before the scheduled appointment. Participants will have up to 5 days prior to their appointment to access the link and complete the questionnaires. Participants who have not completed the assessments and questionnaires electronically prior to the visit will be asked to complete the assessments and questionnaires during the visit.

PHQ-9. Depressive symptoms will be assessed using the PHQ-9 during screening. The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. This assessment is brief and useful in clinical practice, as it can be completed by the patient in minutes and be rapidly scored by the study staff. It can also be scored repeatedly, which can reflect improvement or worsening of depression in response to study procedures. Thus, this assessment can be administered at any visit if the participant reports depressive symptoms (see Appendix I).

GAD-7. Generalized anxiety will be assessed using the self-administered GAD-7 during the screening session. This assessment has 7 items that can be scored immediately by the study staff. This assessment can also be administered at any visit (see Appendix I).

ASI-3. The Anxiety Sensitivity Index will be used to identify whether a patient is experiencing a general sense of worry or has specific concerns relating to symptoms of stress (see Appendix GG).

K-6. The Kessler Psychological Distress Scale (K6) is a 5-point Likert scale used as a global measure of distress drawing from depressive and anxiety related symptomology (see Appendix DD).

Mood History Questionnaire. The Mood History Questionnaire is a 16-item self-report assessment that will provide information about the participant's mood in their entire life (see Appendix FF).

CES-D. The Center for Epidemiologic Studies – Depression Scale (CES-D) is a brief self-report scale designed to measure symptoms associated with depression in the past week. The scale includes 20 items comprising 6 scales reflecting major facets of depression: depressed mood, feelings of guilt and worthlessness, feelings of helplessness and hopelessness, psychomotor retardation, loss of appetite, and sleep disturbance (see Appendix EE).

Table 4. Study Time Line and Procedures.

	Table 4. Study Time Line and Procedures								
Study Timeframe		Baseline Screening	Phase 1 Wk 1 (Randomization Visit)	Check -Up Call #1	Phase 2 Wk 2-4	Check-Up Call #2	Phase 3 Wks 5-7	Phase 4 Wks 8-10	30 Day Follow Up Call
Visit #		0	1		2		3	4	FU Call
Study Day	-29	1	8	11*	29	32*	50	71	101
ASSESSMENTS									
Phone Screen (Basic Eligibility)	X								
Informed Consent Signed		x							
Pregnancy Test		x	x		x		x	x	
Expired CO†		x	x		x		x	x	
Height		x							
Weight		x	x		x		x	x	
Urine- Compliance (cotinine, TNE, & MA)			x		x		x	x	
Formaldehyde DNA			x		x		x	x	
Spirometry lung function test†		x						x	
PHQ-9 & GAD-7		x							
Demographics & Smoking History		x							
Medical History		x							
Concomitant Meds		x	x		x		x	x	
Health Changes Questionnaire			x		x		x	x	
Adverse Events			x		x		x	x	
EMA Random Assessments**							x	x	
EMA Daily Diary**					x		x	x	
Product Accountability			x		x		x	x	
TLFB		x	x		x		x	x	x
ASI-3		x							
CES-D		x							
Mood History		x							
K-6		x							
FTND		x							
MNWS		x	x		x		x	x	
QSU - Brief		x	x		x		x	x	
PANAS		x	x		x		x	x	
American Thoracic Society questionnaire (ATSQ)		x	x		x		x	x	
Purchase Tasks – Usual Brand			x		x		x	x	
Purchase Tasks – Study Cigarette					x		x	x	
Purchase Tasks – E-Cigarette							x	x	
Product Evaluation Scales – Usual Brand			x		x		x	x	
Product Evaluation Scales – Study Cigarette					x		x	x	
Product Evaluation Scales – E-Cigarette							x	x	
Implicit Association Tasks			x		x		x	x	
Perceived Health Risks			x		x		x	x	
Instruct to smoke UB		x							
Receive VLNCC			x		x		x		
Receive e-CIG					x		x		
Flavor Testing†			x						
Support/Troubleshoot				x		x			

*if call falls on weekend, holiday or other day when the clinic is officially closed, call may be conducted on next business day; **a troubleshooting call may be conducted if reports show at least 2 consecutive days of no EMA data from subject; †procedure waived during COVID-19

The Demographic, Health and Smoking History Questionnaires. These instruments expand on the data obtained during the pre-screening, providing more detailed information on demographics, health/medication history, alcohol, and other drug use, for use in the medical screening. Information on smoking history (e.g., year's smoked, previous quit attempts, relapse, current smoking rate, and other nicotine/tobacco use) is also obtained. These questionnaires have been used in our previous and current cessation studies to provide descriptive data for the study population (e.g., [158, 159]; See Appendix H).

The Fagerström Test for Nicotine Dependence (FTND). The FTND is a 6 item questionnaire that measures nicotine dependence by assessing various components of smoking behavior such as daily intake, difficulty in refraining from smoking, and time to first cigarette [98, 160]. In some studies, the scale has been found to correlate with cotinine level [37, 38] and to predict smoking treatment outcome [161]. It was modified from the most commonly used nicotine dependence measure, the Fagerstrom Tolerance Questionnaire [162]. Time to first cigarette (within 30 minutes) has been noted to be the item accounting for the majority of the variance in this scale and the one most highly correlated with multidimensional scales of nicotine dependence [163] (see Appendix Q).

The Positive and Negative Affect Scale (PANAS). The PANAS [102] is comprised of two 10-item mood scales: Positive Affect (PA) and Negative Affect (NA). Participants rate different feelings and emotions on a scale of 1-5. Various time instructions (e.g., today, past few days, past week, general, etc.) have been used with acceptably high alpha reliability ranging from .86 to .90 for PA and .84 to .87 for NA. Post-cessation PANAS negative affect is a robust predictor of relapse [164, 165] (see Appendix S).

Questionnaire on Smoking Urges -- Brief Version (QSU).The QSU Brief Form is a 10 item validated questionnaire measuring desire and intention to smoke; and anticipation of relief from negative affect and desire to smoke. The QSU has been found to be predictive of craving in laboratory studies [101] and lower scores on each of the subscales have been noted for smokers treated with varenicline or bupropion in the original clinical trials of varenicline [166] (see Appendix W).

Minnesota Nicotine Withdrawal Scale (MNWS). The MNWS is a 15-item measure of nicotine withdrawal symptoms (see Appendix R).

E-Cigarette Type Images. Subjects will indicate which types of e-cigarette they have used in the last 30 days before screening (see Appendix VV).

Abstinence. Abstinence data will be collected at all contacts using a timeline follow-back (TLFB) procedure [95, 167] as we have done in our previous studies [168]. In addition to cigarette smoking, we will also use the TLFB procedure to measure the use of other forms of tobacco and nicotine, such as cigars and e-cigarettes. Abstinence outcomes conform to the Society of Research on Nicotine and Tobacco (SRNT) [169] guidelines (see Appendix N).

Participant Compensation.

Following randomization, participants will be remunerated up to $988 plus parking vouchers or metro cards (if available) for completing all visits and assessments from baseline/screening through the end of the study. This includes up to $378 for completion of all EMA assessments, up to $300 in compliance bonuses, and up to $40 for at-home urine collection (up to $30 for in-person visits and up to $40 for virtual visits) and a $30 return phone bonus for returning their study phone in working order (including the accessories that were issued with the phone like charger, cord, case and screen protector, etc.). In an effort to reduce clinic burden, when the Ver 7 revision is approved, We will begin sending questionnaire links to participants in advance of their in-person scheduled clinic visits and offering a $10 bonus ($50

total max) if they complete electronically prior to coming in to the clinic visit. If the visits are conducted virtually, participants will be offered a $10 bonus ($40 total max) for providing saliva/cheek swab samples.The current compensation scheme has been adjusted accordingly and will only affect newly consented participants after the revision is approved (this includes those newly consented with phone bonus revision as well). Those that already signed consent under the previous scheme will be compensated according to the previous scheme. See Appendix Y. for the Compensation Schedule. Participants will receive their monetary compensation in the form of a reloadable Bank of America card that is issued to them at the baseline screening visit and reloaded at subsequently completed vistis (see Appendix D).

Medication Blinding

The blinding will be handled by the Tobacco Research and Treatment Program's database management team. The master key linking the actual treatments with the blinded codes will be maintained by the database team. The database team will write and maintain the software that conducts the randomization of research participants, including the minimization procedure being used for subject stratification and random assignment. Study staff randomize the study participant after all eligibility criteria are met and recorded in the database (by design the program will not work otherwise). The group assignment is displayed to study staff who assigned the medication as blinded code. Blinded reports are available that provide information on the distribution of factors within treatment group as a cross check on the program's accuracy. Study team members (data managers and senior staff) not involved in direct subject care will have access to randomization assignments. We have implemented this process in several other protocols.

Breaking the Blind

Un-blinding of single cases by the investigator will only be performed if relevant for the safety of the participant. The PI along with the Program Director (PD) will be responsible for implementing procedures for maintaining the blind and for breaking the blind when necessary. The PI must notify the IND Medical Monitor/Office prior to the un-blinding of a participant. In emergency situations, the Principal Investigator (PI) would consult with the Program Director (PD) and/or the research team's Data Management Supervisor (DMS) to obtain immediate blinding information for the participant. The PD/DMS would then pass this information on to the PI to enable the participant to be treated. In non-emergency situations, the same procedures would apply, however the PI and PD will discuss and evaluate the request, then, the PI after consulting with the study physician would be responsible for making the decision of whether or not to un-blind. When the blinding code is broken, the reason will be fully documented and included on the appropriate data collection forms. After a subject completes the study, they can be provided with their medication assignment(s) if requested.

Potential Risks

Adverse Experiences Associated with Physiological Assessments

Participants may also experience potential tobacco withdrawal effects (e.g., increased irritability, difficulty concentrating, etc.) during VLNC usage. None of these effects typically result in serious adverse health consequences.

Adverse Experiences Associated Questionnaires

It is unlikely that completing questionnaires would lead to any potential risks for participants, although some participants may be uncomfortable answering certain questions. To the extent these are required for study participation (i.e. psychiatric and medical history), patients who do not wish to answer will not be eligible for participation. It is highly unlikely that any legal, social, or psychological problems will result from this research. In the event a

participant experiences a mental health emergency (e.g. suicidality, etc.) procedures outlines in the Mental Health Procedures (Appendix Z) will be observed.

Adverse experiences associated with lung spirometry

Spirometry is a forced expiratory assessment that is generally safe. The most common adverse experience is dizziness, the incidence of which would cause the procedure to be paused, per guidelines [124]. However, spirometry does acutely increase blood and thoracic pressure, and is contraindicated for myocardial infarct, pulmonary embolism, ascending aortic aneurysm, and recent major thoracic, abdominal, or head surgery [170]. Participants will be screened for these conditions and may be disqualified from pulmonary function testing if they have a history of any of these conditions. Severe adverse events are not expected for spirometry, but in rare circumstances, this can cause syncope or near syncope.

Adverse Experiences Associated with Nicotine Abstinence/Withdrawal

Participants may experience nicotine abstinence/withdrawal effects. These effects may include irritability, difficulty concentrating, insomnia, anxiety, dysphoria, and increased hunger. None of these effects result in serious adverse health consequences.

Adverse Experiences Associated with VLNC cigarettes

The cigarettes used in this study have been used in previous studies including the ongoing U54 discussed in preliminary studies, with no untoward adverse effects or significant increase in expired CO and other toxicants [28, 31]. All participants will undergo a review of their medical history prior to randomization and will be monitored throughout the study for potential adverse events. Potential side effects with VLNC cigarettes are similar to what might be expected from smoking their own cigarettes which have long term health consequences that are not enhanced by the short term use of VLNC cigarettes in this study. Compensatory smoking may occur which could lead to increased toxicant exposure, although in our current trial and in previous studies compensatory smoking was shown to be minimal and higher levels of toxicant exposure were generally not observed [28, 29, 31]. While 6 subjects in our interim analysis showed a CO >50 ppm, none were on the .03 mg/ml dose used here. Nevertheless we will follow the guidelines developed for the U54 for reporting adverse events for an increase in carbon monoxide levels. An adverse event will be reported if the CO is greater than 60 ppm for participants with baseline CO of less than 35. An average two CO readings of 100 ppm or greater will result in automatic withdrawal.

Adverse Experiences Associated with e-cigarettes

The short and long-term risks of using e-cigarettes are currently unknown. The most common side effects are changes in taste, dehydration, mucus in the throat/sinus, dry mouth, dry cough, throat irritation, sore throat, mouth ulcers, dizziness, headache, and nausea. However, it is possible that e-cigarettes may cause lung injuries or other serious health problems, as indicated by recent alerts by the CDC [81] and the Texas Department of State Health Services [84]. Some people who use e-cigarettes have reported experiencing seizures. Some of these individuals reported a prior history of seizures or using other substances at the same time as their e-cigarette. In addition, in many cases e-cigarette use has led to respiratory illnesses such as difficulties breathing, shortness of breath and/or chest pain before hospitalization. In some cases, e-cigarette use has led to death, possibly due to lipoid pneumonia, and the CDC has advised people to stop vaping. In some cases, symptoms of mild to moderate gastrointestinal illness such as vomiting, diarrhea, or fevers or fatigue have been reported. We will inform study participants of these risks and that they should monitor yourself for symptoms (e.g., cough, shortness of breath, chest pain) and promptly contact the study staff they are experiencing such symptoms. We will also inform participants to call 911 if they are experiencing a potentially life-threatening emergency.

E-cigarettes may also increase nicotine dependence. If stored improperly (e.g., in a pocket or where the device can turn on accidentally), overheating of the device may occur, which presents a minor burn risk.

Study medical monitor Dr. Karam-Hage and his team will monitor for respiratory and other adverse events, along with our collaborator from the Department of Pulmonology, Dr. Ostrin. The study team will receive email updates about the vaping-related lung injury epidemic from the CDC and the Texas Department of State Health Services (see Appendix XX for examples of these updates). However, it should be noted that The Texas Department of State Health Services (DSHS) weekly update on 2/10/2020 [84] stated that the "CDC is discontinuing data collection on February 18, 2020" concerning lung injury related to e-cigarette use. The final CDC report strongly linked the EVALI illness to THC cartridges that were adulterard with vitamin E acetate [85]. Regardless, the study coordinator (or designee) and Dr. Robinson will continue to receive and review the Texas DSHS and CDC alerts as long as they are published throughout the duration of this protocol. In the event of a new health risk associated with the electronic cigarettes used in this protocol that is identified by these weekly alerts, we will take the following steps: (1) the newly identified risk will be discussed within 5 days by study chair Dr. Paul Cinciripini, collaborator and Study Physician Dr. Maher Karam-Hage, pulmonology collaborator Dr. Ostrin, and collaborator Dr. Robinson to determine its relevance to the study products used in this protocol; (2) if the risk is deemed by the collaborators to be related to the study products used in this protocol, we will contact all active subjects by phone within 5 days and submit a PI memo to MD Anderson's IRB and IND offices that describes this new health risk (also within 5 days); (3) Upon determination by the IRB, the protocol and ICD will be revised to incorporate information about the newly identified risk, the DSMB will be informed at the next semi-annual review of this protocol, and active participants will be reconsented with the details of these new risks. We will keep a log of any new risks communicated by the CDC and/or the Texas HHS that are deemed relevant to the study products used in this protocol, including participants who are contacted and/or reconsented and the date of this contact. Note that CDC and Texas HHS monitoring of vaping-related lung injuries ended in February 2020.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Participants will be recruited from the state of Texas areas and/or Houston community sample using: (1) mail, public service announcements, radio, print and digital advertisements including social media and other applications, media interviews, MD Anderson Internet access, , MD Anderson Conquest Magazine; (2) through the MDACC community liaison and outreach offices, sending advertisements, and mailers to all affiliated providers on the mailing list. All advertising will be approved by MD Anderson’s Strategic Communication and Marketing Departments. Consent will be obtained at the onset of the orientation/baseline interview. Participants will be provided with a detailed description of the study, information on risks, and on their right to withdraw from the study.

Protection Against Risks

Our procedures closely follow those used in our previous clinical trials and include medical and psychiatric screening. Our study medical provider will identify participants who are medically unstable and unsuitable for participation in the study. While we expect little procedure related adverse events we will monitor participants for any adverse reactions (related and unrelated) throughout the study (see Appendices HH).

Adverse effects and concomitant medications will be assessed at each of the post-baseline visits. Participants’ CO, and weight will also be measured at each in-person assessment. During the COVID-19 pandemic, we will temporarily waive collecting participants’

CO and will collect height and weight via participant self-report. The study medical provider will monitor participants' complaints of adverse events and order any follow-up procedures (laboratory assessments, etc.) as required. Adverse experience assessments will continue until 30 days following completion of the VLNC+ E-Cigarette phase.

Study medical monitor Dr. Karam-Hage and his team will monitor for respiratory and other adverse events, along with our collaborator from the Department of Pulmonology, Dr. Ostrin. Dr. Ostrin will oversee spirometric interpretation and quality control for the duration of the trial and will be consulted by Dr. Karam-Hage on respiratory-related AEs, as needed.

Confidentiality will be protected by identifying all subjects by ID numbers in all data used outside the institution (e.g., laboratory assessments). Analyses of such data are provided by sample number coded on each collection container and cannot be connected to individual participant names by the laboratory conducting the assays. Only the PI and his staff will have access to the master file linking laboratory and other data to participant names. All study data files are server maintained with limited access using password entry and log in restrictions to study staff. All information will be reported in aggregate form and individual participants will not be identified in any public reports or documents. We expect these procedures to be highly effective for protecting participant confidentiality.

Study product accountability plan

Inventory control will be managed by the study team and overseen by the Program Director. Specifically, custody and distribution of the JUUL device and the JUUL pods will be tracked from date of receipt into inventory at the study site through unique identifiers (serial numbers and batch codes) assigned by the manufacturer. The JUUL device Serial Number is a unique combination of eight characters (letters and numbers) engraved on the back of your device, below the JUUL logo. JUUL serial numbers only use the number 0 (zero) and not the letter O (as in Oscar). The JUULpod Batch Code is on the back of the packaging, just below the perforation and on the reverse side of the JUULpod foil blister pack. The alphanumeric number is between 6-12 characters. The devices and pods will be tracked on a log with a staff signature and date of distribution to the study participant as well as the date of return to the study site by the participant. The blinded nicotine level of the distributed JUULpods will be coded by a custom-developed code and will be placed on each pod. The custom code will contain the Subject ID, nicotine strength, and the date distributed. See Appendix YY for the tracking template.

The distribution of the eGo device and cartomizers will be tracked on a log indicating the date, manufacturer's batch number and "best used by" date as well as the number of cartomizers dispensed and the number of cartomizers returned. The log will also indicate the blinded staff member responsible for dispensing the cartomizers to the clinic research staff.

Study product will be stored in locked cabinets with keys assigned to designated study staff.

Potential Benefits of the Proposed Research to the Subjects and Others

While there is no assurance that the individual subject will benefit from participation, their study experience could lead to a greater awareness of their smoking patterns, a reduction in cigarette consumption and/or a possible cessation attempt. For those that do wish to make a cessation attempt at the conclusion of the study, a community referral or opportunity to participate in one of our smoking cessation trials will be provided.

Importance of the Knowledge to be Gained

The potential benefit to society as a result of this study will be to add to the body of evidence needed for successful regulation of nicotine products. The overall goal of such

Table 5. Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Unlikely	Phase I	Phase I	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Possible	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Probable	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Definitive	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III

regulation is to improve the public health by reducing nicotine dependence and toxicant exposure. As no data yet exist on the effects of combining VLNC and e-cigarette on nicotine dependence and toxicant exposure, there is the potential for this study to have a significant benefit to society .These potential benefits outweigh the risks associated with the proposed research.

Data and Safety Monitoring Plan

The IRB of The University of Texas MD Anderson Cancer Center (MDACC) reviews and approves the Data and Safety Monitoring Plan for all clinical trials. This protocol will be monitored by the MDACC IND Office according to a protocol-specific monitoring plan that will be created for this trial**.**

Adverse Event Monitoring & Concomitant Medication.

Participants will be assessed for side effects and concomitant medications using standard FDA guidelines recommended for these two procedures and recorded into the project database. Adverse event terminology and grades will be determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, published by the U.S. Department of Health and Human Services.

A response time matrix will be used to guide the medical team on how long they have to respond (immediately to 48 hours) to the notice of an adverse event based on its rating. If someone from the medical team deems it clinically appropriate, the medical team or study staff may provide the subject with patient education materials printed from the MD Anderson database related to the AE they are experiencing. The subject will not be taken off study product unless the study physician or his/her personal physician recommends that we do so. Participants reporting chest pain or chest pressure will be administered a Chest Pain/Chest Pressure questionnaire (see Appendix F.) and will be triaged accordingly.

Adverse events will be reviewed by our medical personnel and the PI. Adverse event monitoring will continue up to 30 days after medication is completed. If an AE is spontaneously reported after the AE reporting period is over, the AE will be recorded in the patient's progress notes. Those AEs that are probably, possibly or definitely related to treatment will be followed until resolution or end of study, whichever comes first. In the case of reports of suicidal ideation, depression or anxiety which we believe may be related to treatment, if possible, we will engage in our normal psychological assessments. The Addiction Psychiatrist will determine the course of clinical management according to methods of good clinical practice. The PI or physician is responsible for determining the attribution of adverse events to study medication.

For this trial, AEs will be recorded according to the Recommended Adverse Event Recording Guidelines for Phase III protocols (see shaded areas of the **Table 5**). Based on the

new safety information related to vaping and e-cigarette use, this protocol will be reviewed every 6 months for safety monitoring by IRB Continuing Review and MD Anderson's Data Safety Monitoring Board (DSMB).

Serious Adverse Event Reporting (SAE) Reporting MD Anderson IND Office Guidelines

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience - any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Data Quality and Integrity

Participants' patient health information (PHI) will be entered into the Tobacco Research and Treatment Program (TRTP) database (APPID-264846) maintained by in-house data programmers. Adverse events and concomitant medications will also be entered into this database. Study questionnaires will be administered using Qualtrics, a Web-based survey development tool that is used primarily to create and administer surveys, store data and conduct analysis. Qualtrics has been vetted by MD Anderson's Compliance, Legal and Information Security departments and it meets all guidelines of the Health Insurance Portability and Accountability Act (HIPAA) and Family Educational Rights and Privacy Act (FERPA). Participants will sign a Qualtrics Acknowledgement form acknowledging any Qualtrics session they completed in-person. Staff may sign a form acknowledging completion for sessions completed electronically by the participant prior to the visit (see Appendix MM).

F. INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women

Women will comprise approximately 50% of the targeted sample. In our previous research, we encountered no difficulty in recruiting women participants.

Inclusion of Minorities

According to the U.S. Census Bureau (2010), the population of the state of Texas from which the sample will be drawn (including Harris County) is estimated at 28,995,881 people. The ethnic distribution has been reported as 42% white, 12% African American, 5% Asian, and 40% Hispanic or Latino (of any race). We expect to recruit minority smokers in proportion to the population demographics and CDC 2009 smoking prevalence. We have had good success in recruiting from ethnic minority populations, especially African Americans, across all of our studies. Our success with Hispanic smokers has been more modest, although it must be noted that smoking rates are lower in the Hispanic and Latino community compared with rates in the non-Hispanic community.

If needed, we may also attract minority smokers to the proposed study by using direct public service advertisements targeted to minority smokers on Houston radio stations and newspapers supporting a large minority audience. Houston has two television stations and several radio stations and newspapers that serve the Hispanic community. The Office of Public Affairs at MD Anderson has also agreed to assist us by arranging for our participation in institution-wide cancer prevention outreach programs directed at the Hispanic community. Such events are sponsored several times a year in areas of the community with high concentrations of minority Houstonians. We will focus additional recruitment effort on these venues to increase our recruitment of Hispanic smokers. Such efforts will be in addition to the normal interviews, advertisements, and news releases conducted on our behalf by the Office of Public Affairs at MD Anderson.

COVID-19 adaptation: While this study is being conducted virtually, we will expand participant recruitment to the state of Texas.

G. INCLUSION OF CHILDREN

We will exclude smokers younger than 21 years of age because the focus of the parent study is on adult smokers, and because Texas law changed to raise the minimum legal age for purchasing and using tobacco products to 21 as of 9/1/2019. The characteristics of smokers previously recruited in similar experiments have been very consistent in our recruitment as well as in national samples. The average age of these smokers is older than 40 years; they consume about a pack of cigarettes or less per day, have made numerous quit attempts, and have smoked for more than 15 years. Significant differences between adults and adolescents are likely in several domains, including attentional and physiological response to nicotine and nicotine cues. Therefore, the study of the brain mechanisms associated with smoking behavior among adolescent smokers would require a separate focus on those factors that are relevant for this population.

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