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Gender Differences in Standardized Research E-Cigarette (SREC) Product Use, Acceptability, Reinforcement, and Nicotine Dependence Symptoms

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Table of Contents

A. OBJECTIVES

The objective of this National Institutes of Health (NIH)-funded proposal is to characterize potential gender differences when switching from combustible cigarettes (CCs) to nicotine and placebo experimental electronic cigarettes, the National Institute on Drug Abuse's (NIDA) Standard Research E-Cigarettes (SRECs). We propose the following aims:

Aim 1. To characterize the effects of switching to nicotine vs. placebo SRECs from CCs on product use, product acceptability, reinforcement, and nicotine dependence symptoms among adult daily CC smokers. We hypothesize that nicotine-containing SRECs (SREC-NIC; 5%; ~59 mg/ml nicotine) will lead to decreases in CC-specific measures, decreases in withdrawal symptoms, and increases in electronic cigarette (EC)-specific use, acceptability, and reinforcement compared to placebo SRECs (SREC-PLA; 0 mg/ml nicotine). The primary outcome measure for Aim 1 will be CPD.

Aim 2. To characterize the differences between male and female CC smokers when switching to nicotine vs. placebo SRECs from CCs on product use, product acceptability, reinforcement, and nicotine dependence symptoms. We hypothesize that men, compared to women, will show more product use, acceptability, and reinforcement with SREC-NIC, relative to SREC-PLA, but that women will show overall less SREC use, and less CC reduction, than men. The primary outcome measure for Aim 2 will be CPD.

Exploratory Aim: To characterize which factors moderate or mediate the effects of switching to nicotine and placebo SRECs from CCs among male and female CC smokers. In an exploratory fashion, we will examine whether baseline factors, including prior EC exposure/ flavor preference, menthol CC preference, nicotine dependence, exposure (nicotine, cotinine, anabasine), hormonal contraception use, age, and race/ethnicity, moderate the Aims 1 & 2 hypotheses. We will also examine the mediating effects of product satisfaction, menstrual phase, and smartphone-collected withdrawal, craving, affect, product use on these hypotheses.

B. SIGNIFICANCE AND INNOVATION

Significance

This project will provide NIDA with critical information on potential gender differences during the switching to nicotine and placebo Standard Research E-Cigarettes (SRECs) from combustible cigarettes (CCs) in terms of product use, product acceptability, reinforcement, and nicotine dependence symptoms among adult daily CC smokers. Additionally, this project is significant because it will examine the impact of SREC use separately for men and women, who are known to respond to CC products differently on measures of product use, product acceptability, reinforcement, and nicotine dependence symptoms. Ultimately, this proposal will help inform NIDA and the scientific field the extent to which the SRECs are useful models of electronic cigarette (EC) use for both men and women.

While ECs are growing rapidly in popularity [1], the variety of devices and device components [2] make evaluating ECs a "moving target." By commissioning the creation of the SREC, NIDA has created a potential "reference" EC that can be used to generate more comparable data between studies. While the SREC has nicotine levels comparable to commercially popular JUUL products (5%; ~59 mg/ml), the SREC is only available in "tobacco" flavor, a flavor which relatively few EC users prefer, particularly among young adults [3]. Our proposal will investigate factors that will the potentially moderate or mediate SREC use and acceptability.

In terms of gender differences, there have been relatively few studies that have examined them in relation to EC use and acceptability, particularly with regards to specific EC

characteristics. However, there is evidence from CC users that suggests that there are gender differences in terms of what nicotine product factors influence use, acceptability, reinforcement, and dependence. For example, men have been found to be more sensitive to nicotine content than women e.g., [4-6], which suggests that male CC smokers may be more likely to use and accept EC products that produce nicotine content similar to CCs. Women, compared to men, have been found to be more influenced by sensory aspects of smoking [7] and to have expectancies about smoking's role in controlling negative affect [8] and weight maintenance [9]. Thus, these findings suggest that there may be characteristics of the SREC that differentially impact their use and acceptability, by gender.

Scientific Premise

Justification for our research is based on the following observations and hypotheses from the EC and tobacco literatures: (1) EC variety makes it a moving target in need of a standard model, (2) EC prevalence is increasing and is subject to dual use, and (3) male and female CC smokers may have different responses to ECs. Additionally, our preliminary studies provide support for the feasibility of our approach. These contentions are developed in the Justification and Feasibility section, below.

Innovation

This project is innovative because it will be among the first to evaluate gender differences in the effect of switching from CCs to use of SRECs adult smokers using a prospective clinical trial. Additionally, we will take a multi-level approach to distinguishing between the effects of SREC (either nicotine [5%; ~59 mg/ml nicotine; SREC-NIC] or placebo [0 mg/mL nicotine; SREC-PLA]) from usual brand (UB) CCs on the domains of product use (cigarettes/day [CPD], nicotine, cotinine, and a tobacco-specific minor alkaloid [MAs; anabasine, nicotelline]), product acceptability (explicit product liking, implicit product liking, perceived product harm, and product-specific expectancies [i.e., perceived outcomes of product use]), product reinforcement (relative reinforcing efficacy [RRE]), and nicotine dependence symptoms (CC dependence, EC dependence, nicotine withdrawal, craving, and affect). The positive impact of this study will be to provide scientific information on whether the SREC is found to be used and accepted by CC smokers, whether it reduces reinforcement and nicotine dependence symptoms among CC smokers, and whether it could serve as a good model of future EC research for male and female users.

C. APPROACH

Justification and Feasibility

Review of Relevant Literature

EC variety makes it a moving target in need of a standard model. ECs (also known as electronic nicotine delivery systems; 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 [10]. The technology is rapidly changing and many types of ENDS are available [2]. NIDA's Standard Research E-Cigarette (SREC), a second generation-type device, is designed to provide a standardized platform for studying ECs [11]. This proposal is in response to a 2-year FOA (PAR-18-220) to encourage evaluation of the SREC.

EC prevalence is increasing and is subject to dual use. In a recent and comprehensive survey assessing use, prevalence, and demographics, Zhu and colleagues [10] found that the prevalence of ever and current use of ECs 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% & 0.2%, respectively) and

never smokers (1.0%, & 0%, respectively). In a study of nearly 6,000 people from the US, UK, Canada, and Australia, Adkison and colleagues [1] found that nearly half of the sample were aware of EC products, and the prevalence of trying ECs was higher among younger, nondaily smokers with a higher income who perceived such products as less harmful than traditional cigarettes. Current EC use was highest among nondaily and heavy smokers (>20 CPD) [1]. Dual use appears to be most common among current smokers who were considering quitting in 6 months [12], as well as among young adult smokers aged 18-24 [13]. A sizeable number of EC users continue to smoke combustible cigarettes [12,14], with nearly half reporting EC use in situations where they can't smoke [10]. Most smokers who report using ECs in the last 30 days do not report using them daily [10]. 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 [15]. Thus, preliminary evidence suggests that most daily CC smokers who try ECs are not likely to completely switch to them and instead become dual users.

Newer Generation IV e-cig products with higher nicotine content, such as the NIDA SREC, may be more reinforcing to adult 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 [16-20].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 [21,22], studies suggest that most e-cigs may not be capable of increasing blood plasma levels as rapidly as smoking CCs [23,24]. Most e-cig users reported using between 4 mg/ml and 24 mg/ml nicotine concentrations [25]. Farsalinos and colleagues [21] 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 [21,26]. Preliminary data suggest that the high-dose nicotine salts in generation IV e-cigs such as the NIDA SREC (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 [27]. Thus, we believe that offering smokers high nicotine-dose e-cigs, such as the NIDA SREC, may promote their use and acceptability, and reduce the use of CCs.

The NIDA SREC may not be as appealing as commercial ECs due to a lack of flavor options. The SREC is currently available in one flavor, tobacco, which may not appeal to those with prior EC experience or a flavor preference. Most who have tried ECs or who use them routinely prefer flavors other than tobacco, with the most popular flavors being fruit flavors and candy/dessert flavors, with tobacco flavoring being among the least preferred flavor [3]. Flavor preference is particularly strong among young adults [28], as 82.2% of current EC users reported using flavored (i.e., non-tobacco-flavored) ECs, compared to 69.3% of older adults [3]. Additionally, NIDA SRECs are unavailable in menthol flavor, despite the significant number of menthol CC smokers, particularly among minority smokers [29]. Thus, the availability of only tobacco-flavored NIDA SRECs may make them less appealing to CC smokers who have established flavor preferences. It is important to evaluate the SRECs among these users in order to provide a path for future research.

Gender differences in nicotine reinforcement and nicotine withdrawal may influence EC use and acceptability. There is evidence that men are more influenced by nicotine reinforcement than women. Male daily CC users smoke more than women and report greater nicotine dependence [30,31]. However, even among samples of CC smokers who do not differ in smoking amount, men have been found to have higher nicotine levels than women [32], possibly due to men puffing [33] and inhaling [34] more than women. Men have been found to self-

administer nicotine nasal spray more frequently than women [35], use more nicotine gum than women [5], and have been found to be more sensitive to CC nicotine content than women during a progressive ratio reinforcement task [6]. In men, nicotine administration has been found to be more effective in reducing withdrawal symptoms than for women [4,5]. Perkins [36] has suggested that these results suggest that women may be particularly sensitive to the sensory aspects of CC smoking, whereas men may be more sensitive to nicotine dosing. He and his colleagues [7] found that CC olfactory/taste stimuli influenced CC liking and reinforcement more for women than for men. Additionally, another study found that acute craving was reduced by denicotinized cigarettes in female but not male smokers [37]. Taken together, these findings suggest that women may be receptive to SRECs to the extent that they mimic or substitute for the sensory aspects of nicotine, while men may be receptive to SRECs to the extent that they provide nicotine relative to CCs. SRECs, with their single flavor availability, may not be as appealing overall to women than to men, while the SREC-PLA may not be as appealing to men as to women.

Men and women may differ in their response to SREC product characteristics. Population-based survey studies examining gender differences in EC use have yielded equivocal results [38], although one small recent survey study found that female CC smokers who took up ECs were less likely to report completely switching to them than male smokers were [39]. In terms of clinical trials methodology, there have been few published studies that have examined gender differences in response to EC exposure among adult CC smokers. A study exposing CC smokers to a nicotine-containing first generation "cigalike" ECs in the lab found that women rated it as more satisfying than men did [40]. In a brief laboratory exposure to ECs following 1-hr of CC abstinence, men reported significant reductions in craving following nicotine (18 mg) EC use but not to placebo EC use, while women showed no difference by EC dose [41]. In terms of flavor, there is preliminary evidence that women who were switched to ECs for a week with a non-preferred flavor produce lower nicotine concentrations and rate the EC as less likeable than men [42], suggesting that EC flavor may be more important to women in terms of EC use and acceptability. While these clinical trials studies are few and mainly preliminary, they are consistent with the CC literature reviewed above in that they suggest that men are likely to be more responsive to EC nicotine content that women, and that women are likely to be more influenced by non-nicotine factors, such as EC flavor acceptability and similarity of the EC vaping experience to CC smoking.

Gender differences in product-specific expectations may also influence SREC use and acceptability. Some evidence suggests that women have different expectancies (i.e., beliefs) about the impact of smoking than men that might reduce their likelihood of switching to ECs. For example, female smokers, compared to male smokers, have been found to hold expectancies about the weight-controlling benefits of smoking [9], to be more concerned about post-cessation weight gain [43], to identify weight gain as the cause for smoking relapse [44], and to report reduced motivation to quit smoking due to post-cessation weight gain concerns [45]. Compared to men, women have been found to have greater expectancies that smoking reduces negative affect [8], to report smoking in response to negative affect [46], and to believe that smoking cessation will result in increased levels of stress and negative affect [47]. Finally, there is some evidence that women, compared to men, hold less expectancies about the health benefits of quitting smoking [47] and are less motivated to quit because of health benefits [48]. The question is whether these differences in expectancies exist for EC products. For example, if female smokers do not believe that ECs are effective at controlling weight or negative affect compared to CCs, they might be less likely to switch to ECs. Likewise, switching would be less likely to occur if ECs are not perceived as less harmful than CCs. We will assess for potential gender differences in CC and EC expectancies, and evaluate whether EC expectancies measured before and after exposure to SRECs mediate SREC use and acceptability.

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 (1/21/2020) CDC data suggests that this outbreak of lung injury, which began around June 2019 and which peaked in September 2019, has been experienced primarily by individuals vaping oils containing tetrahydrocannabinol (THC), the primary psychoactive ingredient in marijuana [49]. 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 [49]. Many of the samples tested by the FDA and other agencies found evidence of adulterants, including vitamin E acetate [50]. A recent report (12/2019) found vitamin E acetate in the bronchoalveolar lavage fluid of all 48 of 51 individuals with EVALI who were tested using isotope dilution mass spectrometry methods [51]. Additionally, as of 1/27/2020, 90% of those with suspected vape-related lung injury in Texas admitted to vaping THC products [52]. 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 are unlikely to cause adverse events, including those related to lung injury. The CDC appears to be satisfied with this explanation, and discontinued data collection on 2/18/2020 [52]. However, it is possible that e-cigarettes may cause other 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

We have expertise evaluating nicotine product switching. PI Dr. Robinson and Co-I Dr. Cinciripini were Co-I's of a TCORS (CENIC; U54DA031659; Donny & Hatsukami) designed to identify an optimal very low nicotine content (VLNC) cigarette nicotine dose that provides minimal levels of reinforcement and yet remains acceptable to smokers [53]. Non-treatment-seeking smokers participated in a 1-week baseline of UB CC smoking and were then randomized to smoke NIDA research cigarettes [54], ranging in nicotine dose from 15.8 mg/g to 0.4 mg/g per cigarette, or UB CC, for 6 weeks. The data suggest that relative to the UB CC group, those in the VLNC cigarette 0.4 mg/g group smoked fewer cigarettes (7.58 CPD), and importantly, showed a precipitous drop (44%) in total nicotine equivalents (TNE). The 0.4 mg/g group also showed reduced dependency (FTND, minus the CPD item) over the 6 weeks of product use and no compensatory increase in CO, nicotine withdrawal, depression, or other adverse events. However, a significant portion of VLNC users were not compliant with their assigned product, with the majority of those in the 0.4 mg/g VLNC group using their UB CC at least once during the VLNC product use phase [53]. The 2nd U54 project, which involved both Drs. Robinson and Cinciripini, examined whether a gradual or immediate reduction to the 0.4 mg/g VLNC cigarette results in better compliance over 20 weeks of use. Our initial findings suggest that CC smokers can switch to other products, even those with less nicotine, although compliance rates greatly decreased with lower nicotine products.

We have expertise evaluating ECs. PI Dr. Robinson and Co-I Dr. Cinciripini have an active grant that is investigating dual use of ECs and VLNC cigarettes on abuse liability (2015-0638). This R01 will provide the scientific community with critical information on the effects of dual use of VLNC cigarettes and ECs on multiple areas of concern, including abuse liability, nicotine compensation, product use, liking, and reinforcement (relative reinforcing efficacy), and the frequency of and circumstances surrounding dual product use. Many of the same behavioral and nicotine exposure measures that we are using in this funded trial are included in our current proposal, which will allow us to compare across smoking populations.

We have expertise examining gender differences in response to tobacco use. Co-I Dr. Blalock has examined behavioral and cognitive factors that might account for consistent findings of disparities among women in the prevalence of depressive and anxiety disorders [55-57]. She has expertise treating pregnant smokers [58-65]. Dr. Blalock has evaluated smoking behavior and smoking cessation interventions in female gender-disparate populations of smokers, including smokers with comorbid depressive [66,67] and anxiety disorders [68-70]. PI Dr. Robinson examined gender differences to the hedonic properties of nicotine by exposing 12-h nicotine-deprived and nondeprived smokers to nicotine and placebo nasal spray [71]. While both nicotine-deprived men and women produced reduced startle eye blink responding, a measure of aversiveness, following nicotine compared to placebo spray, nicotine nondeprived women showed larger startle eye blinks to nicotine than to placebo spray (there were no startle differences for nondeprived men). These findings suggest that women have a lower threshold for experiencing the aversive qualities of nicotine.

We have expertise using smartphone ecological momentary assessments (EMA) of smoking behavior. Co-I Dr. Cinciripini has extensive experience designing and analyzing EMA data to assess smoking behavior and has previously published on this topic. Our EMA assessment approach permits examining both acute moments and patterns in momentary data (withdrawal, craving, affect) over time [72,73] collected in real-time. Examples of our previous EMA work include demonstrating that abstainers, early lapsers, and late lapsers exhibit significantly different withdrawal trajectories [72], that smokers report higher and more volatile craving to smoke on drinking days [74], and other studies examining smoking outcome expectancies and mood [75-77]. All current EMA work has been assumed by Drs. Robinson, who also has an R01 (R01CA184781) focusing on the use of smartphone technology to reduce attentional bias among smokers.

D. RESEARCH DESIGN AND METHOD

In the current COVID-19 pandemic environment, we will be expanding in-person procedures to a virtual setting, using an institutionally approved platform (e.g., Zoom), which will also allow us to recruit participants state-wide. The following sections have been modified to include the study team's plan for adapting the identified in-person procedures to a virtual setting. However, in-person clinic visits will still be available for participants residing in the Houston area who prefer them.

Overall structure of the study team

The objective of this project is to characterize potential gender differences when switching to nicotine and placebo SRECs on product use, product acceptability, reinforcement, and nicotine dependence symptoms among adult daily CC smokers. This project is an MD Anderson sponsored Investigational Tobacco Product (ITP) study that will be led by PI Dr. Jason Robinson (MD Anderson). The investigative team will include Co-Is Drs. Paul Cinciripini (product switching and tobacco clinical trials expertise; MD Anderson), Janice Blalock (expertise in tobacco-related gender differences; MD Anderson), Maher Karam-Hage (study physician; MD Anderson), Edwin Ostrin (respiratory symptom assessment; MD Anderson), and Sanjay Shete (biostatistics; MD Anderson). Together, we provide the necessary background and intellectual complementarity needed to fulfill all aims of this project. MD Anderson is the sole site and will perform all administrative, data coordinating, and participant enrollment functions. Nicotine, cotinine, and anabasine will be analyzed by collaborator Dr. Peiying Yang, Associate Professor of Integrative Medicine Research at MD Anderson. The collaborators will meet weekly with the research staff throughout the duration of this project.

Recruitment and Retention Plan

Study participants will be individuals residing in the State of Texas. Recruitment efforts may include direct mail from registries, mailing flyers, public service announcements, media interviews, and advertisements on online social media, radio , television, and newspaper outlets (see Appendix R), and digital advertising companies. Institutional channels may be used to aid study recruitment, including, but not limited to, patient database data mining (e.g., EPIC, TRTP database) for potentially eligible patients and other internal recruitment methods (e.g., MyChart to send messages, newsletters, inside MD Anderson television channels). 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. We will rotate through various venues throughout the recruitment period. We have many years of experience using these venues for quitting and nonquitting tobacco clinical trials recruitment. The MD Anderson Marketing and Communications departments may also assist in arranging interviews, public service announcements, and social media communications to assist in study recruitment. Additionally, we may engage the services of external clinical trials recruitment services to obtain contact information of prospective study participants. We anticipate no difficulty in recruiting the required number of participants.

Table 1. Inclusion Exclusion Criteria.

Inclusion Criteria:
- Aged 21 years or older
-Reports being a daily or non-daily smoker (any self-reported smoking in the past 30 days)
- Have an address where he/she can receive mail
- Able to follow verbal and written instructions in English and complete all aspects of the study as determined by PI
- Willing to have urine biospecimen samples taken, either in-home and returning them by mail, or in-person at an approved collection site.
- Willing to use tobacco-flavored study electronic cigarettes
-Agrees to comply with all MD Anderson institutional policies related to COVID-19 screening prior to any in-person research visit.
-The individual agrees to not engage in study procedures or interactions with study personnel while operating a vehicle.

Exclusion Criteria:
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- Individuals who report depressive symptoms in the moderately severe or severe range on the PHQ-9 (scores of 15 or above) or who report current suicidal ideation on the PHQ-9
- Uncontrolled or unstable medical condition (e.g., uncontrolled hypertension, angina, diabetes).
- Evidence of cognitive deficits or instability that would preclude reliable study participation.
-Being pregnant, engaging in breast-feeding, or being of childbearing potential and engaging in sexual activity that could lead to pregnancy and is not protected by a medically acceptable, effective method of birth control while enrolled in the study, as determined by self-report. Medically acceptable contraceptives include: (1) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, or (3) an intrauterine device (IUD). Contraceptive measures sold for emergency use after unprotected sex are not acceptable methods for routine use.
- Considered by the investigator to be an unsuitable or unstable candidate (including but not limited to the following situation: unwilling or unable to comply with study procedures)
-Individuals who reside in an area that is outside of our shipping company's area of operation or in a jurisdiction outside of our medical staff's licensure (if unable to attend in-person clinic visits) AND who decline or are unable to come in to clinic to provide necessary samples and/or collect study products.

To facilitate participant retention and compliance with study procedures, we will offer financial compensation. Enrolled participants will have the opportunity to receive a potential maximum compensation of $522 each (see Appendix V). Participants will be compensated up to $25 for each in-person or virtual visit (up to $100) (excluding the telephone AE follow-up), up to $40 for completing

study questionnaires prior to visit ($10/instance), $2/instance for completing short message service (SMS)-prompted once daily smartphone Qualtrics assessments of product use for 42 days (up to $84), and $2/day for completing random smartphone EMA assessments (completed 2 times/day) for 42 days (up to $168). Additionally, we will provide $50 to participants at the end of both phases 2 & 3 contingent upon the return of all used and unused SREC cartridges (up to $100 total). We have used this EMA compensation scheme successfully in other studies, obtaining over 75% response rate to individual EMA assessments. We also use automated text messaging to remind participants of appointments and provide feedback on missed EMA assessments. Also, because participants will be asked to use their personal smartphone devices and personal data plans for study related assessments, they will receive an additional $30 at the end of study participation. Participants without a smartphone, or who would prefer not to use their own device, may be provided with a smartphone and service plan for the duration of the study. For this group, they will receive the additional $30 for returning the smartphone at the end of study participation. Participants wil not be compensated for the final safety telephone call since no research assessments will be administered. Payment for the visits will be issued either upon receipt of the samples at MD Anderson or upon shipping package tracking showing sample movement back to our clinic.

COVID-19 adaptation: No adaptations needed.

Participants

We will recruit up to 196 participants (98 male and 98 female adult CC smokers) from the state of Texas and/or Houston metropolitan areas. Inclusion/exclusion criteria are described in **Table 1**. 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.

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 (see Appendix S) by a trained study staff member to determine initial eligibility (e.g., age, interest in trying ECs). Women of child-bearing potential will be asked about pregnancy and lactation status and contraception use at phone screen. In the event a female subject becomes, or is found to be, pregnant while active in the study, the subject will be withdrawn from the protocol, referred to their primary care physician (PCP), and will be offered smoking cessation counseling at that time.

Eligible participants will be scheduled for the initial screening visit (V0), which may be done in-person or virtually through an institutionally approved platform (e.g., Zoom). 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, they will be automatically connected to questionnaires hosted on MD Anderson’s Qualtrics platform, prior to their scheduled screening visit. Participants may receive a phone call, email, and/or text message before their laboratory or virtual sessions to remind them of the appointment. Eligibility criteria including age, CPD, stable address, interest in trying ECs, and pregnancy-related criteria will be collected through self-report during the telephone screening.

COVID-19 adaptation: As applicable during the SARS-CoV-2 pandemic and recovery phase, MD Anderson institutional screening requirements will be reviewed with the participant and their verbal acknowledgement obtained before scheduling the in-person screening visit.

In-person or virtual screening session (V0). The consenting staff member will review the Informed Consent Document and all relevant study information. They will then review any questions the patient may have, and confirm that they understand the nature of the research being performed. Fluency in spoken and written English will be assessed by a TRTP study staff member during the consenting process by asking the participant to read aloud a section of the Informed Consent Document. This will be noted in the Documentation of Informed Consent. Additionally, information provided at the time of the phone screen may be verified prior to consent.

Participants will be instructed to smoke *ad libitum* prior to this session. Prior to the session, the participant will be asked to complete basic demographics, smoking, tobacco product use, and health history questionnaires used in our previous studies [78] that will be reviewed and approved for eligibility by a licensed medical provider following the visit. CC, SREC, and other tobacco product use eligibility criteria will be evaluated using a timeline follow back procedure [79] and smoking history measures used in previous studies [80]. These questionniares may be pushed by our institutional Qualtrics server to be completed electronically (via text or email) prior to the session. Current major depressive disorder (MDD) and suicidality will be identified using the Patient Health Questionnaire (PHQ-9; see Appendix L) [81].The screening session and the three return visits are each expected to last approximately 3 hours. The final safety telephone call will assess any ongoing adverse effects and should last approximately 10 minutes.

COVID-19 adaptation: Eligible participants will be scheduled for a virtual screening session using an institutionally approved platform, such as Zoom. If we are unable to collect any required biological specimens through mail, the participant may be asked to go in-person to conduct the tests through an approved collection site. Approved sites may include University of Texas MD Anderson, University of Texas sister institutions including the Center for Neurobehavioral Research on Addiction (CNRA) at University of Texas Medical School, other universities or hospitals located in Texas, and/or contracted commercial vendors.

Baseline Medical Clearance. Following the completion of the baseline visit, a member of the medical team (Physician assistant and/or the Physician) will review all relevant data collected at screening and will provide their clearance for the participant to proceed to Visit 1. The study Physician will have the final review of the data and will complete the final eligibility sign off prior to randomization. In the event the Physician is not able to sign-off prior to the visit (due to being out of office), the Principal Investigator may provide the initial sign-off so that the visit may proceed, and the physician will sign-off upon their return.

Following the medical team clearance to proceed to Visit 1, a study supply kit will be sent containing the urine specimen collection supplies and other study materials.

Study Supply Kit: Baseline Screening Visit. The following items are incuded in the initial study supply kit:

- Written instructions
- Urine collection kit
- Reloadable gift card (e.g., Bank of America or another approved institutional option)
- Return address label, postage-paid, and box for shipment
- Biospecimen bag, absorbant test tube sleeves

The study specific supplies wil be shipped to eligibile participants and tracked through eShipGlobal or a comparable system within two business days of completion of the Baseline

Screening Visit. Mailing time may be adjusted due to carrier delays, holidays, or any other factor impacting delivery time. Written instructions will be provided and the research team will be available to guide participants through the sample collection process as needed. The participant must complete and return the required samples to the MD Anderson research team prior to Visit 1, or Visit 1 may be rescheduled.

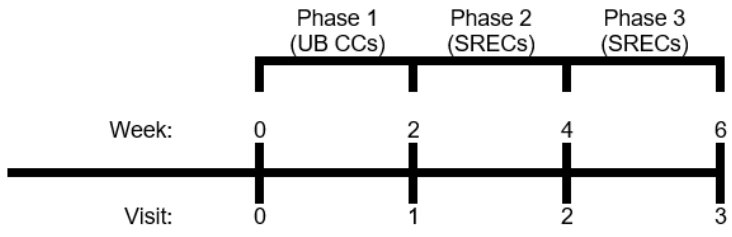
Phase 1: UB Baseline (weeks 1-2). During this phase, participants will be instructed to smoke their usual brand *ad libitum*. Measures specific to this phase will be captured at a virtual or in-person visit at the end of week 2. Daily smartphone EMA assessments, as described below, will occur throughout Phase 1. Refer to **Figure 1** for a timeline of study procedures.

COVID-19 adaptation: No adaptations needed.

Phases 2 & 3: SREC-NIC and SREC-PLA use (weeks 3-4, 5-6). During Phases 2 & 3, participants will be provided with SREC-NIC or SREC-PLA, in a counter-balanced fashion (i.e., half will receive SREC-NIC during phase 2 and SREC-PLA during phase 3). The subjects will be randomized on a 1:1 ratio and will be assigned to their randomization group through the protocol specific TRTP database. 50% (70 subjects) will receive the Active study product first and the placebo second and 50% will receive the Placebo study product first and the active study product second. During the randomization process, participants will be stratified by gender for order of exposure to SREC-PLA and SREC-NIC. At the beginning of each phase, each participant will receive 2 SREC devices with non-removable rechargeable batteries (3.3 v, 1000 mAh battery), 1 USB recharger, a 2-week supply of sealed SREC tanks (14 pods; containing either nicotine or placebo e-liquid), a user manual, and a carrying pouch. The SRECS are produced by NJOY LLC (Glenns Ferry, ID) under NIDA contract, and are available in two nicotine doses, 5% (~59 mg/ml nicotine) and 0% (0 mg/mL nicotine; placebo), a single flavor (nicotine), and in sealed disposable pods that deliver <350 puffs/pod [11]. Participants will be instructed to use the SREC during Phases 2 and 3 whenever they get the urge to smoke, but will not be penalized for using their UB CCs or other nicotine products (including other ECs), as product use is a dependent measure in this study. The use of UB CCs and the study products will be documented daily by the participant in Qualtrics as part of the EMA.

At the beginning Phase 2, participants will receive training in how to use the SREC product. They may be shown a brief video demonstrating its use followed by a hands-on training which will include assembly (battery and tank), turning the SREC on and off, puffing, and recharging the battery. The training session will last 30 minutes and 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. This procedure is currently being used by us in our active EC grant (R01DA042526), and has been found to result in users achieving cigarette or near-cigarette levels of blood nicotine among EC-naive CC smokers in other studies [82]. The study staff will receive instruction on the use of the SREC device by the Program Director. The training will be documented on Protocol Training Logs and will be stored in the regulatory binders for monitor review.

Figure 1. Timeline of study procedures.



NOTE. Participant assignment to SREC type at phases 2 and 3 will be counter-balanced within group, with half of men and women receiving the placebo SREC during Phase 2. During all phases, participants will complete daily EMA assessments.

Participants and study staff will be blind to SREC

condition. The Program Director, who will not have participant contact, will manage the inventory and labeling of blinded products. Blinded study staff will distribute the product to patients at each visit. The study medical monitor (Dr. Karam-Hage) and collaborator on respiratory symptom assessment (Dr. Ostrin) will be provided unblinded information on SREC condition by the Program Director, per their request. In the case an unblinding needs to occur, the study team will notify the IND sponsor Clinical Trials Safety Team, the DSMB, and the IRB. The SRECs will be obtained through NIDA's procurement process.

Measures specific to these phases will be captured at in-person or virtual visits at the end of each phase (weeks 4 & 6). Daily smartphone EMA assessments will occur throughout all phases.

COVID-19 adaptation: Participants will be mailed their 2-week allotment of study ECIGs prior to the start of phases 2 and 3 by a study staff member blinded to the nicotine dose. Additionally, participants will be asked to provide the urine samples during each phase and mail those back to the primary MD Anderson site. All supplies to collect the samples, as well as shipping materials and postage will be provided. Visit payment will be issued once MD Anderson staff are able to track movement on the return package. Alternatively, participants may be asked to collect the study ECIGs and/or provide their urine samples in-person from an approved site. Approved sites may include University of Texas MD Anderson, University of Texas sister institutions including the Center for Neurobehavioral Research on Addiction (CNRA) at University of Texas Medical School, other universities or hospitals located in Texas, and/or contracted commercial vendors.

Study Supply Kit: Treatment visits. The following items are included in each treatment visit study kit.

- Urine collection kit
- Return address label, postage-paid, and box for shipment
- Biospecimen bag, absorbant test tube sleeves
- e-cigarette kit
- Written instructions

Treatment study kits will be mailed approximately 5-7 days prior to each treatment visit. Mailing time may be adjusted due to carrier delays, holidays, or any other factor impacting delivery time. Participants will be instructed to complete the required visit samples and place in the mail to be returned to MD Anderson.

Adverse Event Safety Assessment. 30 days (+/- 7 days) following the end of Phase 3, study participants will complete a telephone visit with study staff to assess ongoing adverse events.

Post-study smoking cessation treatment. We will offer all participants 8 weeks of free smoking cessation treatment, which may include nicotine replacement therapy (NRT; nicotine patch and lozenge) and smoking cessation counseling, at the end of their study participation. Alternatively they may be referred to another smoking cessation study. It is not the intention of this phase of study to evaluate the efficacy of EC for smoking cessation, but rather to facilitate smoking cessation by offering free treatment at the conclusion of EC exposure. This fulfills what we see as a strong ethical obligation to treat smokers that enter our research programs. NRT and counseling will be administered by MD Anderson's Tobacco Treatment Program (TTP), headed by Drs. Cinciripini (Co-I) and Karam-Hage (Co-I), which provides free treatment to all

Table 2. Project measurement, by time point.

Week	-1	0	2	4	6	10
Visit	**T0**	**0**	**1**	**2**	**3**	**T1**
Telephone contact	x					x
In-person or virtual Session		x	x	x	x	
Initial baseline measures:						
Initial eligibility screen (e.g., age, nicotine product use)	x					
Demographics, smoking, tobacco product use, and health history		x				
PHQ-9		x				
Tobacco Products and Risk Perceptions Survey (TPRPS)		x				
Environmental Tobacco Smoke Exposure Questionnaire (ETSEQ)		x				
Product Use:						
Timeline Follow Back (TLFB) of CC & other product use		x	x	x	x	x
Timeline Follow Back (TLFB) of SREC use				x	x	
Urine sample to measure nicotine, cotinine, nicotelline and anabasine			x	x	x	
Smartphone EMA of product use[1]		x	x	x	x	
Ongoing Adverse Event (AE) Assessment				x	x	x
Health Changes Questionnaire			x	x	x	
Product Acceptability:						
Product Evaluation Scale (PES) - CC		x	x	x	x	
Product Evaluation Scale (PES) - SREC				x	x	
Perceived Health Risk Questionnaire (PHRQ) – CCs & ECs		x	x	x	x	
Perceived Health Risk Questionnaire (PHRQ) – SRECs				x	x	
Implicit Association Test (IAT) – CCs & ECs		x	x	x	x	
Brief Smoking Consequences Questionnaire-Adult (BSCQ-A)		x	x	x	x	
EC-specific Brief Smoking Consequences Questionnaire-Adult (EC-BSCQ-A)		x	x	x	x	
Product Reinforcement:						
Purchase task (PT) - CCs		x	x	x	x	
Purchase task (PT) - SRECs				x	x	
Respiratory Health and Symptoms						
American Thoracic Society questionnaire (ATSQ)		x	x	x	x	
Nicotine Dependence Symptoms:						
Fagerström Test for Cigarette Dependence (FTCD)		x	x	x	x	
Penn State Electronic Cigarette Dependence Index (PSECDI)				x	x	
Minnesota Nicotine Withdrawal Scale-Revised (MNWS)		x	x	x	x	
Positive and Negative Affect Scales (PANAS)		x	x	x	x	
Questionnaire of Smoking Urges-Brief (QSU-Brief)		x	x	x	x	
Smartphone EMA of nicotine dependence symptoms[1]		x	x	x	x	
Other:						
Assess Contraception use		x	x	x	x	
Update Menstrual Phase information		x	x	x	x	
Note. [1]Smartphone EMA will be assessed daily throughout the 6-week study period;						

MD Anderson patients, family members, and employees, or by the Tobacco Treatment Program Quitline, also headed by Dr. Cinciripini. The TTP has a 9-month cessation rate of 36%-47% [83]. An alternative options would be a referral to a cessation trial, based on availability.

Measures

The behavioral measures described below will be obtained at baseline (week 0) and the end of each phase (weeks 2, 4, and 6), except for smartphone EMA, which will be collected daily in each participant's home environment throughout the 6 weeks of study participation. All questionnaires will be administered using MD Anderson's Qualtrics platform. Missed visits and associated assessments will be recorded in the study database, but will not be logged as protocol deviations because they are expected in smoking cessation trials. In our previous tobacco-related trials over the past 20 years, we have found that participants only attend about 75% of scheduled sessions. Refer to **Table 2** for a list of the project measurement domains and assessments.

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 (see Appendix BB). Alternatively, community participants may be asked to provide a urine sample at an approved collection site within a week of their scheduled virtual "in-person" visits. Approved sites may include MD Anderson, University of Texas sister institutions including the Center for Neurobehavioral Research on Addiction (CNRA) at University of Texas Medical School, other universities or hospitals located in Texas, and/or contracted commercial vendors. TLFB will be collected virtually by study staff. We will also provide postage-paid shipping supplies for participants to return all used and unused e-cig pods. Questionnaires will continue to be administered electronically via the institutionally-approved web-based Qualtrics platform administered over the study smartphones.

Demographics, smoking, tobacco product use, and health history. As part of the screening session, and to capture information for the exploratory aim, participants will complete basic demographics, smoking, tobacco product use, and health history questionnaires used in our previous studies (see Appendices C and I) [78]. Menthol CC preference will also be captured. Recent (past 30 days) and prior EC use and EC flavor preference (if ECs have been used in the

past) will be collected using the EC items of the Tobacco Products and Risk Perceptions Survey (TPRPS; see Appendix P) [3], a survey developed by the Georgia State University Tobacco Center of Regulatory Science (TCORS) [84]. We will also collect participants' exposure to cigarette smoke at home and at social setting using the Environmental Tobacco Smoke Exposure Questionnaire (ETSEQ) at the screening session.

At visits 0, 1, 2, and 3, we will collect self-reported information on hormonal contraception use and menstrual phase (estimated from the start date of the last menstrual period) in premenopausal women. Because withdrawal symptoms may influence product switching, we will examine these factors as potential mediators in our analyses (Exploratory Aim). Both being in the luteal phase, compared to follicular phase [85], and use of hormonal contraception have been found to increase nicotine withdrawal symptoms [86]. Because these are exploratory factors, we elected to not collect blood at every session for hormonal confirmation using progesterone, or to exclude women with factors that would influence these factors (e.g., being post-hysterectomy or post-menopausal).

Assessment of product use. As part of Aims 1 & 2, we will collect measures of CC and EC product use and exposure. At each visit, study staff will complete a Time Line Follow Back (TLFB; see Appendix O) [87] interview to record nicotine product use since their last visit, including daily CC use (all phases; CPD), SREC use (Phases 2 & 3; SREC sessions/day), and other nicotine product use (all phases; including other tobacco and non-study EC products). Participants will be required to return used and unused SREC sealed pods at weeks 4 and 6 for product accounting.

During each phase, participants will provide a urine sample to measure total nicotine equivalents (TNE) and the tobacco minor alkaloids (MA) anabasine and nicotelline, which will be analyzed by Dr. Peiying Yang, associate professor of Integrative Medicine Research at MD Anderson, using liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) [91,92]. TNE is the sum of total nicotine, cotinine, 3'-hydroxycotinine, and nicotine N-oxide excreted in urine ("total" refers to the analyte and its glucuronide conjugate), comprising 85 to 95% of the nicotine dose received by a tobacco user [93]. Use of TNE will enable us to quantify changes in nicotine exposure throughout the study. The MAs anabasine and nicotelline will allow us to estimate differential use in combustible vs. EC use, because MAs are almost exclusively derived from tobacco, and not nicotine [94].

During all phases, participants will complete SMS-prompted once daily smartphone Qualtrics assessments of product use (CPD, number of EC episodes [Phases 2 & 3], other tobacco use) and 2 daily random assessments of nicotine dependence symptoms (withdrawal, craving, and affect; see Assessment of Product Reinforcement, below). For the daily assessments of product use, the SMS will arrive on the participant's smartphone approximately 2 hours before his or her self-determined bed time, and will contain a link to a questionnaire provided through MD Anderson's Qualtrics survey platform. The random EMA assessments of nicotine dependence symptoms will be restricted to 2 instances per day to limit participant burden. To do so, each day will be divided into 2 blocks, based on each participant's reported wake and bed time that is collected at the screening visit (see Appendix X). Our SMS/Qualtrics backend software, running on a Microsoft SQL Server, will prevent random assessments from occurring within 2 hours of other assessments. The *primary* outcome measure of Aims 1 & 2, CPD, will come from the smartphone daily diary data of CC use over the past 24 hours. TLFB collected at each phase will be used as a secondary source of CC use to supplement missing smartphone daily diary data.

The total time to complete the once daily product use and 2 random EMA assessments of nicotine dependence symptoms will be approximately 15-20 minutes/day. Our previous

research has obtained EMA compliance rates of >75% [72,74] and found EMA reactivity to be nonexistent or small [95]. 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 [72,74,96]. Because prompts may occur at inconvenient times (e.g., driving), participants will be instructed that they can delay responding for up to 90 minutes, and they will receive a "missing assessment" SMS reminder if they fail to complete a daily or random assessment within 90 minutes of it being sent. The SMS/Qualtrics app will provide feedback on percentage of completed assessments, as well as compensation earned (see Recruitment and Retention Plan, above). We have successfully used this SMS/Qualtrics platform to collect similar EMA data in our current EC/VLNC product switching grant (2015-0638). Participants without a smartphone, or who would prefer not to use their own device, will be provided with a smartphone and service plan for the duration of the study. Given that 77% of adults own smartphones, as of 2016 [97], we anticipate that relatively few participants will need a study smartphone.

Assessment of product acceptability. As part of Aims 1 & 2, product acceptability will be evaluated in terms of explicit product liking, perceived product harm, and implicit product liking (i.e., attitudes) at the end of each phase. Explicit product liking will be measured using Product Evaluation Scales (PES), which are modified versions of the Cigarette Evaluation Scale (CES) [98]. The CES is an 11-item questionnaire that evaluates the cigarette smoking experience in terms of satisfaction, tastiness, dizziness, ability to calm, concentration, wakefulness, reduction of hunger, nausea, irritability, enjoyment of sensations of smoke, and craving reduction. We will use 2 product-specific versions of the PES to evaluate CC and SREC product liking (with SRECs evaluated at weeks 4 & 6 only; see Appendix M).

To assess perceived product harm, we will administer modified Perceived Health Risk Questionnaires (PHRQs; see Appendix K) [99] that will assess participants' beliefs about their risks of developing lung cancer, emphysema, bronchitis, other cancers, heart disease, risk of addiction, and stroke on a scale of 1 (very low risk of disease) to 10 (very high risk of disease). These scales will be modified so that participants will assess the perceived risks associated with their UB CCs and ECs (i.e., electronic cigarettes "in general") at each time point, and a SREC-specific version at weeks 4 & 6 only.

To assess implicit product liking, participants will complete 2 Implicit Association Tests (IAT) designed to evaluate attitudes towards CCs and ECs during each phase (see Appendix Q). The IAT has been used to evaluate attitudes toward consumer products [100,101] 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. ECs + 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 [102]. We have substantial previous experience with this task using established methods in our studies [103]. We are currently using this task in our active EC study (2015-0638). For both products of interest, we created 24 pictures that minimize product branding, and the good and bad attribute words came from a previously published set from our lab [104]. To score the IAT, we will use the standardized difference score (D) method [105]. Each IAT product comparison will take approximately 8 minutes to complete.

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

To assess product-specific expectancies (i.e., perceived outcomes of product use), we will administer the Brief Smoking Consequences Questionnaire-Adult (BSCQ-A) [106] to assess CC-specific expectancies (see Appendix F) and the EC-specific Brief Smoking Consequences Questionnaire-Adult (EC-BSCQ-A) [107] to assess EC-specific expectancies (see Appendix G). Both are 25-items questionnaires that assess beliefs (i.e., expectancies) about what happens when they smoke CCs (BSCQ-A) or use ECs (EC-BSCQ-A) on 10 scales, including Negative Affect Reduction, Stimulation/State Enhancement, Health Risks, Taste/Sensorimotor Manipulation, Social Facilitation, Weight Control, Craving/Addiction, Negative Physical Feelings, Boredom Reduction, and Negative Social Impression, using a 10-point Likert scale (0="completely unlikely" to 9="completely likely"). We will administer these questionnaires at all 4 phases and expect the EC-BSCQ-A to be sensitive to SREC dose (Aim 1) and both to be sensitive to gender differences in expectancies (Aim 2).

Assessment of product reinforcement. As part of Aims 1 & 2, we will assess CC and SREQ product relative reinforcing efficacy (RRE) using two separate product-specific purchase tasks (PT) at each in-person or virtual visit (with SRECs evaluated at weeks 4 & 6 only; see Appendices D and E). PTs are behavioral economic reward valuation tasks that have been used to assess the RRE of food [108], alcohol [109], illicit drugs [110], and nicotine products [111]. PTs provide an estimate of how much a participant is willing to pay (i.e., its valuation) for a given product (UB, SREC) 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 between CCs and SRECs to determine their RREs.

Assessment of nicotine dependence symptoms. As part of Aims 1 & 2, participants will complete questionnaires assessing nicotine dependence symptoms, including CC dependence (Fagerström Test for Cigarette Dependence [FTCD; formerly the FTND; see Appendix C]) [112,113], EC dependence (Penn State Electronic Cigarette Dependence Index [PSECDI; see Appendix J]) [114], nicotine withdrawal (Minnesota Nicotine Withdrawal Scale-Revised [MNWS; see Appendix H]) [115], affect (Positive and Negative Affect Scales [PANAS; see Appendix I]) [116], and craving to smoke (Questionnaire of Smoking Urges-Brief [QSU-Brief; see Appendix N]) [117] at each study visit.

During all phases, SMS/Qualtrics will be used to collect 2 daily random smartphone EMA measures of nicotine dependence symptoms, including nicotine withdrawal, craving, and affect, based on 8 items from the QSU, PANAS, and MNWS. Further details about the 2 daily smartphone EMA measures, as well as the once daily assessments of product use, are described above in the "Assessment of product use" section.

Assessment of respiratory and other symptoms. We will also assess respiratory symptoms at each visit using the American Thoracic Society questionnaire (ATSQ) [118]. The ATSQ is an 8-item questionnaire that assesses symptoms including coughing, wheezing, phlegm production, shortness of breath. An email will be sent to project staff when a participant completes the ATSQ and has a total score of >3 on questions #4-8. Staff will assess symptoms with the participant at the next visit. If symptoms present prior to the start of study product (V0 or V1), staff will add the conditions to the medical history. If the elevated score presents while on study product, staff will assess changes in symptoms and severity and log an adverse event, if indicated.

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. The physician may delegate to other members of the medical team the task of a preliminary review of the adverse event, attribution, and recommended action plan. The physician will then complete the final review of the adverse event, confirm attribution and sign off on the adverse events.

Statistical Approach & Expected Outcomes

General Data Analytic Strategy. To analyze our aims, we will use a crossover design model [119] with n = 140 subjects (assuming 15% attrition of n=164) and k = 3 periods. In this design, t_0 and t_1 will be the two SREC types, with t_0 for SREC-PLA and t_1 for SREC-NIC. We will use the following model for *y (e.g., CPD):* $y_{ij} = b_1 + b_{2t(i,j),t(l,j-1)} + e_{ij}$, where b_1 is the effect of subject *i, and* b_2 is the effect of treatment t_{01} when preceded by treatment t_{10}. $T(i,j)$ is the treatment assigned to subject i in period j, for $1 \le i \le n$ and $1 \le j \le k$. The residual errors e_{ij} are assumed to be independent and identically distributed with expectation 0 and variance σ^2. In this design, each subject will act as its own control reducing the influence of confounding, reducing variance and improving accuracy and sensitivity for the estimated effect of interest. In the interaction models (Aim 2), gender will be entered in the equation and interacted with $b_{2t(i,j),t(l,j-1)}$ to estimate gender by treatment interaction effects on all outcomes. Period and carryover effects will be evaluated by testing equivalence of effects across time (e.g., CPD collected using TLFB). We will utilize a mixed model approach for estimation using the "glmer" function of the "lme4" R package [120]. Missingness will be treated as missing-at-random within maximum likelihood estimation and we will utilize not-missing-at-random approaches (e.g., pattern mixture model) if non-ignorable missingness is suspected [121,122]. Given the large number of outcomes, the analyses will address issues of multiplicity by applying the False Discovery Rate [123].

Hypothesis Testing: Aim 1. To characterize the effects of switching to nicotine vs. placebo SRECs from CCs on product use, product acceptability, reinforcement, and nicotine dependence symptoms among adult daily CC smokers. Assessments will include: product use (CPD, number of EC vaping sessions, nicotine, cotinine, minor tobacco alkaloids); product acceptability (explicit product liking, implicit product liking, and perceived product harm); reinforcement (RRE) and nicotine dependence symptoms (withdrawal, craving, and affect). We hypothesize that SREC-NIC will lead to decreases in CC-specific measures (CPD, minor tobacco alkaloids, and CC dependence), decreases in withdrawal symptoms, and increases in EC-specific use, acceptability, and reinforcement compared to SREC-PLA. The primary outcome measure for Aim 1 will be CPD.

Hypothesis Testing: Aim 2. To characterize the differences between male and female CC smokers when switching to nicotine vs. placebo SRECs from CCs on product use, product acceptability, reinforcement, and nicotine dependence symptoms. This aim will examine the moderating role of gender on the impact of SREC type on the assessments described in Aim 1. We hypothesize that men, compared to women, will show more product use, acceptability, and reinforcement with SREC-NIC, relative to SREC-PLA, but that women will show overall less SREC use, and less CC reduction, than men. The primary outcome measure for Aim 2 will be CPD.

Exploratory Aim: To characterize which factors moderate or mediate the effects of switching to nicotine and placebo SRECs from CCs among male and female CC smokers. In an exploratory fashion, we will examine whether baseline factors, including prior EC exposure and prior flavor preference, menthol CC preference, nicotine dependence, baseline TNE, and race/ethnicity, moderate the Aims 1 & 2 hypotheses. We will also examine the potentially mediating effects of product satisfaction, hormonal contraception use, menstrual phase, and smartphone-collected withdrawal, craving, affect, product use on these hypotheses.

Power and Sample Size

Our power analyses were conducted using a sample size of n=140 total participants. However, we will recruit and randomize n=164 because we expect a 15% drop-out rate by Week 6, based on the attrition rate of our existing EC product switching protocol (2015-0638).To demonstrate that we have adequate statistical power to detect likely effect sizes with n=140, we conducted power analyses for Aim 1 (i.e., the main effect of SREC type) and Aim 2 (i.e., the interaction between gender and SREC type) on our primary outcome measure, CPD collected from TLFB. However, in our attempt to estimate likely CPD effect size differences by gender as a function of SREC exposure (Aim 2), we were limited because there were no published studies that reported gender differences in CC and EC product use among CC smokers who were switched to nicotine and/or placebo ECs. Instead, to estimate the effect size of switching from CCs to ECs on CPD, we used a study [124] that examined the impact of switching to 18 mg ECs over 2 weeks that found that participants reduced their CPD by 96.3% (16.2 to 0.6 CPD). This allowed us to estimate the impact of switching to an EC with nicotine amounts similar to that of the SREC. To estimate the impact of product nicotine dose and gender on CPD, we used a study [125] that examined the impact of switching CC smokers to either VLNC (0.05 to 0.09 mg nicotine yield) CCs alone or combined VLNC cigarettes and NRT (21 mg patch). While this study did not include ECs, it allowed for the examination of the impact of nicotine on CPD, by gender, and found that men in the nicotine group (VLNC+NRT) smoked less VLNC CCs at week 2 than women [125].

Because of the absence of reliable effect sizes of the interaction effect under study in the literature, we estimated power for a series of effect sizes for both the direct and indirect effect. To perform the power analysis we first generated the matrix for our crossover design using the "samplingDataCRT" R package to sample data that reflects our prospective analysis. After generating the sample data, we calculated power for both the main effect of SREC type on CPD (Aim 1) and the SREC type by gender interaction (Aim 2) using three steps: 1) generate new CPD values from the crossover model defined above, 2) refit the model to the simulated data, and 3) evaluate the true positive success rate using the "simr" package [126]. We ran 1000 simulations for each estimation for a series of effect sizes and for both the main effects and interaction models. **Figure 2** presents the power curves of these analyses. For the gender by SREC type interaction (Aim 2), **Figure 2** indicates that we have 80% power to detect a difference of 3.5 CPD or larger between the genders during SREC-NIC. For the SREC type main effect (Aim 1), **Figure 2** (inset) indicates that we have 80% power to detect a difference of 1.75 CPD or larger between SREC-NIC and SREC-PLA. The minimal detectable effect size is larger for the interaction effect compared to the main affect due to the increased power required to detect subgroup effects in randomized trials [127,128]. Since the main modeling framework is linear, the interaction effect under study has an additive interpretation, such that the combined effects of SREC-NIC and being male contributes more to CPD reduction than the individual effects of the two factors. Additive interaction effects are more relevant for public health decision making and require a lower sample size than multiplicative interaction effects [129]. In conclusion, our proposed sample size of 140 provide enough power to detect a CPD change of 1.75 for the main effect of SREC type and a CPD reduction of 3.5 for the proposed interaction effect, which we believe will be adequate to detect the likely differences we would observe.

Potential Problems & Alternative Strategies

It is possible that the NIDA SREC use rates and product acceptability may be low in this study. Potential reasons for this have been described above, including (1) a lack of SREC flavors other than nicotine despite evidence that most EC users prefer flavors other than tobacco [3], (2) a lack of menthol SREC flavoring despite the ubiquity of menthol CC use among ethnically diverse populations [29], and (3) a level of nicotine in the SREC-NIC that, while comparable to other commercial ECs [11], may produce nicotine pharmacokinetics that are less reinforcing for DCS than those of CCs [21,26]. One way to increase higher NIDA SREC use rates would be to incentivize their use, such as by paying participants a bonus if specific biomarkers indicated no CC product use (e.g., using anabasine, which is derived from tobacco and is not affected by EC use) [94]. However, we elected to evaluate NIDA SREC use without incentivizing it because we are seeking to provide NIDA with "naturalistic" information about SREC use and acceptability, as dependent variables, among a diverse sample of male and female adult CC smokers. We believe that even if SREC use and acceptability are low, this information would be of importance to NIDA.

The lengths of the SREC dose phases (2 weeks each) could be insufficient to determine stable responding. However, one study that switched CC users to ECs, using a within-subjects design, found that 2 weeks product exposure resulted in significant associations between EC nicotine dose and CPD, EC product use, and craving [130]. Additionally, in our prior TCORS study we observed that most changes occurred within the initial 2 weeks of product use among CC smokers who were administered experimental CCs, including VLNC cigarettes [53]. These findings suggest that 2 weeks of SREC exposure should be adequate to capture changes in response to switching to these novel nicotine products.

Despite the lack of a menthol-flavored SREC, we decided to include menthol smokers in this study. A significant number of minority CC smokers prefer menthol [29], and preliminary evidence suggests that adult menthol CC smokers prefer menthol over tobacco-flavored ECs [131]. Additionally, menthol smokers typically represent ~55% of the community participants recruited for our non-treatment-seeking nicotine studies [132]. Thus, to exclude menthol smokers would reduce the generalizability of the SREC findings in terms of use and acceptability.

This proposal will not include biochemical confirmation of menstrual phase or hormonal contraception use, and instead will rely upon self-report (e.g., menstrual phase estimated from start of last menstrual period), unlike other similar studies [85]. In studies that use biochemical verification, most use serum measures of progesterone and estradiol levels to more precisely differentiate the luteal from the follicular phase [133]. We also will not exclude women using hormonal contraception, despite the impact of such contraception on the menstrual cycle. We elected not to collect serum hormone levels at each phase because we do not want to burden or expose participants to the risks associated with 4 blood draws for what we consider to be exploratory factors in this project. Similar reasoning led us to not exclude women taking

Figure 2. Power Curves (and 95% confidence intervals) for the Gender by SREC type Interaction Effect (Aim 2; main plot) and for the main effect of SREC type (Aim 1; inset plot).

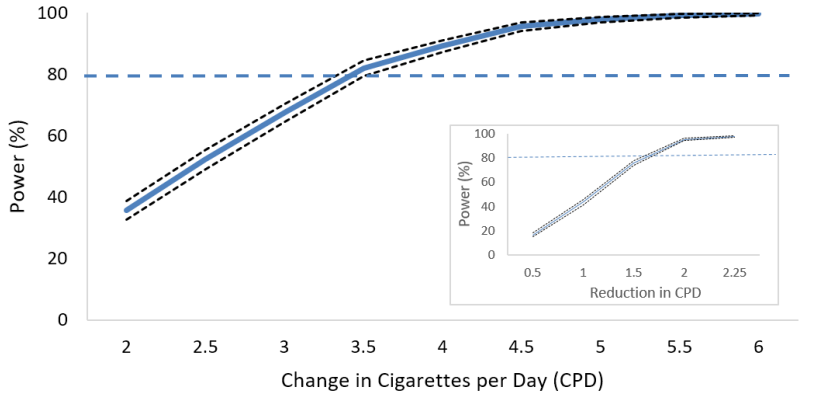


Table 3. Study Timeline.

Study Milestone	*Completion Month*
IRB Approval of Protocol, Database Construction	3 Months
Finalize SOPs, Source Documents, and Staff Training	6 Months
First Participant Enrollment	6 Months
Final Participant Enrollment	20 Months
Complete Final Participant Follow-up	22 Months
Data Analysis & Manuscript Drafting	24 Months

hormonal contraception. However, we will capture self-report of both factors and use them as moderators (hormonal contraceptive use) and mediators (menstrual phase) as part of the exploratory aim.

Safety of EC products. Our current ECIG study suggests that use of a closed-tank ECIG device among adult smokers results in relatively few adverse events. In this protocol (2015-0638; R01DA042526), which is ongoing, we are testing the strategy of simultaneously providing a smoker uninterested in quitting with both VLNCs as well as an ENDS product to determine if they will compensate for the reduction in nicotine from the VLNC's with the ENDS product. This is critical to the regulatory strategy aimed at determining nicotine levels in future ENDS product, because we may wish to maximize compensation in order to move people away from combustibles and increase the likelihood of cessation. 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 study product. 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.

Consideration of Relevant Biological Variables. We will recruit an equal number of male and female adult daily smokers for this study because gender differences form the main focus of this proposal. While biological sex is the primary independent variable, we will also account for other relevant biological variables, such as age, by including them as covariates of interest in our statistical models. We are using multilevel models to partially pool the estimate from each covariate toward the overall mean of all estimates. This is a natural away to account for multiple comparisons without sacrificing power (which we do in the case of Bonferroni correction). Each effect is shrunk toward the overall estimate. The higher the uncertainty of a specific effect the more it shrinks toward the overall estimate.

Timetable. After a 3-month study setup, we expect to enroll between months 6 and 20, at a rate of 10 subjects per month (see **Table 3)**. The final participant session will be during month 22, and data analysis and initial manuscript drafting will occur by month 24.

Future directions. At the project's conclusion, we will be able to provide scientific information on gender differences in terms of the extent to which the NIDA SREC is used and accepted by adult CC smokers, which would indicate whether it could serve as a good model of future EC research. We will also identify factors that moderate or mediate the effects of switching to nicotine and placebo SRECs from CCs. Our next steps will be to submit proposals

Table 4. Recommended Adverse Event Recording Guidelines.

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

that will (1) directly compare longer-term use of the NIDA SRECs to commercial EC devices among EC-naive and experienced male and female dual users, and (2) compare the SREC to EC devices with higher nicotine yields, such 36 mg/ml, a dose that we are using in a current funded study (2015-0638), among male and female adult CC smokers.

E. PROTECTION OF HUMAN SUBJECTS

Risks to the Subjects

Human Subjects Involvement, Characteristics, and Design

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 [134]. We expect to recruit English-speaking minority smokers in proportion to the population demographics, and smoking prevalence. Inclusion and exclusion criteria are listed in **Table 1**. All smokers meeting these qualifications will be accepted into the study. All data collection will occur at MD Anderson Cancer Center.

Study Procedures, Materials, and Potential Risks

Participants will be providing biological samples in the form of urine (nicotine, cotinine, anabasine, nicotelline), and vitals. Questionnaire data will be obtained that assess previous smoking, smoking cessation history, current and past health and psychiatric conditions, mood, CC dependence, EC dependence, nicotine withdrawal, craving, and cigarettes smoked. All data will be collected specifically for research purposes and will be assigned a subject identification number in the Tobacco Research and Treatment Program (TRTP) database and an accession number in CORe to maintain confidentiality. The official database for this study is the TRTP database (APPID-264846) maintained by in-house data programmers. Relevant medical screening data will be shared with the participant as appropriate for referral and follow-up medical care. It is highly unlikely that any legal, social, or psychological problems will result from this research. 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 T. Any individual who is deemed ineligible for study participation for medical/psychiatric reasons will be referred to local medical and/or psychiatric resources.

Adverse Events and Serious Adverse Events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the investigational component even if the event is not considered to be related to study component. Medical conditions/diseases present before starting study component are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. The physician may delegate to other members of the medical team the task of a preliminary review of the adverse event, attribution, and recommended action plan. The physician will then complete the final review of the adverse event, confirm attribution and sign off on the adverse events.Since this is an ITP study, safety will be monitored by the MD Anderson IND Office. Adverse event terminology and grades will be determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, published by the U.S. Department of Health and Human Services. 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 final attribution of adverse events to study medication.

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).

Adverse experiences associated with specimen collection. The collection of urine by the participants using specimen cups are not expected to result in adverse events.

Adverse experiences associated with electronic cigarettes. Use of ECs has been found to increase the risk of acute upper respiratory irritation, cough, phlegm production, headache, dry mouth/throat, vertigo, and nausea [16,20]. Participants using SRECs, particularly the placebo version, may experience nicotine withdrawal effects, including increased irritability, difficulty concentrating, insomnia, anxiety, dysphoria, and hunger. None of these effects should result in serious adverse health consequences. However, 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.

In the event of a new health risk associated with the electronic cigarettes used in this protocol that is identified, 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.

Adverse experiences associated with questionnaires. It is unlikely that completing questionnaires would lead to any potential risks for participants, although some participants may

be uncomfortable answering certain questions and may refuse to do so. To the extent that answers to these questions are required for study participation (e.g., psychiatric and medical history), participants 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.

Specific Instructions for Adverse Events Recording

For this project, adverse events will be recorded according to the Recommended Adverse Event Recording Guidelines for Phase III protocols (see **Table 4**). Relevant medical history and baseline symptoms will be collected at the initial screening visit (V0) and V1, and will be graded according to the CTCAE 5.0 criteria and sent to the medical team for review. Any member of the medical team may review the medical history as part of the pre-randomization review process to clear the participant to V1. The study physician will complete a final eligibility review and sign-off prior to randomization. Adverse events will be recorded starting at every contact once the participant has started study product, which will be V2 and V3. In addition, the participant will complete a 30-day Adverse Event telephone assessment (30 days after V3, with a window of +/- 7 days) to follow up on any ongoing adverse events only.

Serious Adverse Event Reporting (SAE) Reporting

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 24 hours 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 Oncore SAE report form 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 completing the study participation, 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 participation 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.

Reporting to NIDA:

Serious adverse events will be reported to NIDA by the study team. The email address to report SAEs to NIDA is to the grant's Project Scientist, Jana Drgonova, PhD (jana.drgonova@nih.gov) with a CC: to the Program Officer (Evan Herrmann; evan.herrmann@nih.gov).

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.

Adequacy of Protection against Risks

Informed Consent and Assent

All smokers will be prescreened by telephone for basic eligibility requirements. The data will be collected in electronic source document forms through the Qualtrics platform. Qualtrics is an institutionally approved platform for data collection. The data will then be automatically transferred from the Qualtrics platform in to the study specific TRTP database located behind the MD Anderson firewall. Hard copies of the electronic CRFs will be available in the event of any technological difficulties. 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 remain eligible after pre-screening will be scheduled for subsequent combination Informational Session and baseline visit (V0) where the study requirements will be explained in more detail and the informed consent reviewed.

Ideally, the Informational Session will occur within 14 days of the telephone screen but it may occur anytime between the pre-screening phone assessment and the Screening visit (V0). The Informational Session can also be combined with the Screening visit. During this session, the study purpose, other study requirements, side effects and contraindications of the use of ECs will be reviewed. The information presented may be in the form of a slideshow (either paper or electronic), which will be developed by the PIs of the study, and will be based on current studies using ECs 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.

The informed consent document may be sent to the participant by email for their pre-review prior to the scheduled screening visit. During the visit, the consent will be sent to the participant by text and/or email through an institutionally approved platform (e.g., Docusign) and will be signed at the screening visit prior to initiation of any study related procedures and covers a detailed description of the study including all procedures that take place for the duration of study. Paper consent forms may be used as an alternative back-up method during down-time procedures. The informed consent review includes discussion of assessments that are required in order to determine eligibility and are not optional. Participants will be informed that actual study participation requires approval from the study medical team based upon review of screening visit information and medical records (if applicable). Participants will be encouraged to ask questions for understanding and, if in agreement, will sign the informed consent document with the trained staff member. Participants who sign the consent document will be registered into OnCore.

After completing forms required for joining the study, the participant will complete the visit assessments with a trained staff member. If seen in the laboratory, participants will have biospecimens collected in the form of urine (nicotine, cotinine, anabasine, nicotelline), and vitals, using procedures approved by the MD Anderson IRBs. Urine specimens will be collected, stored, and shipped to our collaborators, as detailed in the protocol. If the participant is seen virtually they will complete all questionnaires at the time of the screening visit. If they are seemingly eligibile at the end of the visit, a staff member will mail a study kit to the address on file, containing a reloadable gift card and urine collection supplies. The participant will be instructed on how to complete the required screening urine sample and will be instructed to mail back the urine specimen using the provided pre-paid materials.

Protection against Risks

If an AE is reported, the physician, nurse practitioner, and/or clinical nurse on staff in the MD Anderson Tobacco Treatment Program (TTP) will manage it. The TTP, directed by Co-I's Dr. Paul Cinciripini, and Maher Karam-Hage, provides clinical smoking cessation services to all MD Anderson patients and employees. The TTP medical staff, which includes an addiction psychiatrist, a physician's assistant, a nurse, and several clinical psychologists, participate in clinical trials and laboratory studies as part of their support for tobacco research conducted in the department.

Confidentiality will be protected by identifying participants only by numbers in all data files. Identification numbers will only be connected to individual participant names in a separate file that will be accessible only by the PI and his staff. All study data files will be server-maintained with limited access by using passwords and logins restricted to study staff. All information will be reported in aggregate form, and individual participants will not be identified in any public reports or documents.Data collected from study-provided smartphones will be de-identified and the smartphones will be factory reset when returned to study staff. No data will be destroyed at the conclusion of this study. All data will be housed in the approved TRTP database(s), and data will be locked and de-identified prior to final analysis. We expect these procedures to be highly effective for protecting participant confidentiality. See the "Data and Safety Monitoring Plan" section for further details concerning protection against risks.

Vulnerable Subjects

Vulnerable subjects will not be enrolled in this study.

Potential Benefits of the Proposed Research to Research Participants and Others

While there is no assurance that individuals 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 cessation attempt. For those who are interested in quitting smoking, we will provide 8 weeks of free smoking cessation treatment at MD Anderson's Tobacco Treatment Program after study participation is complete.

Importance of the Knowledge to be Gained

The potential benefit to society as a result of this study will be determine whether e-cigarettes serve as a potentially reduced risk nicotine product compared to combustible tobacco smoking in male and female adult smokers. This proposal will investigate gender differences in the impact of switching to e-cigarettes on adult combustible tobacco smokers, who are currently uninterested in quitting smoking, on a variety of domains, including product use, product acceptability, reinforcement, and nicotine dependence symptoms. These potential benefits outweigh the risks associated with the proposed research.

F. INCLUSION OF WOMEN

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

G. INCLUSION OF MINORITIES

According to the U.S. Census Bureau (2010), the population of the Houston community from which the sample will be drawn (including Harris County) is estimated at 4,070,989 people. The ethnic distribution has been reported as 73% white (35% of whom are not of Hispanic origin), 19% African American, 6% 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.

H. INCLUSION OF CHILDREN

We are not recruiting children because we are targeting adult combustible cigarette smokers who are currently uninterested in quitting but who are interested in trying electronic cigarettes to change smoking behavior, and limiting recruitment to smokers 21 years or older because recent changes to Texas law (as of 9/1/2019) make the use of tobacco products by those younger illegal. Also, children are likely to differ qualitatively and quantitatively from adults in the behaviors and biomarkers of interest. Therefore, a study investigating the transition from

combustible cigarette smoking to electronic cigarette use in children would require a separate focus that accounts for differences in this population.

I. STUDY PRODUCT INVENTORY CONTROL

Inventory control will be managed by the study team and overseen by the Program Director. Custody and distribution of the SREC device and the SREC tanks 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 devices and tanks 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. See Appendix YY for the tracking template. Study product will be stored in locked cabinets with keys assigned to designated study staff.

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