Predictors and Consequences of Combustible Cigarette Smokers' Switch to Standardized Research E-Cigarettes

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Sponsor: National Institute for Drug Abuse (NIDA)

NCT Number: NCT03277495

Version: 9

Date: 5/16/2023

LIST OF ABBREVIATIONS

CO	Carbon Monoxide
DSMB	Data and Safety Monitoring Board
EMA	Ecological Momentary Assessment
ENDS	Electronic Nicotine Delivery Systems
EVALI	E-cigarette, or Vaping, Product Use Associated Lung Injury
FDA	Food and Drug Administration
ITP	Investigational Tobacco Product
IRB	Institutional Review Board
NIDA	National Institute of Drug Abuse
OPRS	Office for the Protection of Research Subjects
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SBIR	Small Business Innovation Research
SREC	Standardized Research E-Cigarette
UIC	University of Illinois at Chicago

1.0 Project Summary/Abstract

Combustible tobacco use remains the primary cause of cancer morbidity and mortality in the United States, and a major cause of cardiovascular and pulmonary diseases. Although there has been tremendous progress in reducing cigarette smoking, approximately 15% of adults over age 18 in the U.S. currently smoke cigarettes, and progress with smoking cessation appears to be stalling. To reduce the substantial toll from cigarette smoking, we need to consider a variety of approaches to more rapidly reduce its harm, especially for smokers who are not motivated or ready to stop smoking or who have been unsuccessful in quitting with current cessation treatments. The primary purpose of this study is to examine whether conventional, combustible cigarette smokers can reduce their use of cigarettes and associated harms by switching to an e-cigarette (Standardized Research E-Cigarette or SREC). This project will use Ecological Momentary Assessments (EMA) to gather real-time, naturalistic reports of conventional smokers' use and experience of a SREC as they attempt to switch from combustible cigarettes to SREC. We will examine how the proximal contexts and subjective experiences surrounding SREC use differ from smokers' patterns and responses to conventional cigarette use, and how these differences may predict success in switching. In addition, we will assess in-depth, in real time, smokers' reports of urges and withdrawal symptoms as they switch to a SREC. We will also evaluate changes in health and biomarker variables. We will enroll a sample of 120 adult combustible cigarette smokers who are interested in switching to an e-cigarette. Participants will complete a baseline one-week EMA wave while they are smoking their usual cigarettes, complete baseline assessments, and then will be randomized (within sex) in a 1:1 ratio to either usual flavor SREC pods or free choice of flavors SREC pods. Participants in the usual flavor condition will receive either tobacco (regular smokers) or menthol (menthol smokers) while those in the free choice condition can choose from the following flavors: tobacco, menthol, watermelon, and blueberry. Participants will receive brief behavioral counseling about reducing cigarettes and switching to the SREC. After one week of using a SREC, they will complete another EMA week to assess patterns and responses to use of both the SREC and cigarettes. Participants will receive 12 weeks of SREC supplies; complete daily reports of product use along with bi-weekly check-ins through the end of the 12-week trial, and then complete a one-month follow-up. Our aims are to: 1) Examine whether conventional cigarette smokers can significantly reduce their combustible cigarette use by switching to SREC; 2) Examine whether reductions in conventional cigarette use and uptake of SREC are associated with changes in health and biomarker variables; 3) Examine smokers' subjective responses to SREC in real time, as they are used, and whether these responses are associated with cigarette reduction; and 4) Examine how patterns of use (e.g., contexts, timing) and subjective experience with SREC differ from conventional cigarette use, and whether differences are associated with success in switching to SREC. Data from this study will provide valuable information about the potential for harm reduction if cigarette smokers switch to a SREC.

2.0 Background/Scientific Rationale

Combustible tobacco use remains the primary cause of cancer morbidity and mortality in the United States, and a major cause of cardiovascular and pulmonary diseases.[1] Although there has been tremendous progress in reducing smoking, 15% of adults in the U.S. currently smoke cigarettes.[2] To reduce the substantial toll from tobacco, we need to consider a variety of approaches to more rapidly reduce its harm, especially for those smokers who may not be motivated to stop smoking or who have been unsuccessful in quitting. The primary purpose of this study is to examine whether combustible cigarette smokers can reduce their use of cigarettes and associated harms by switching to a SREC. Smokers continue to smoke primarily because of the nicotine. Yet most of the morbidity and mortality associated with cigarette smoking comes not from the nicotine, but rather, from a variety of toxins and constituents that result from the combustion process.[1] E-cigarettes or Electronic Nicotine Delivery Systems (ENDS) may provide an alternative way for smokers who are unable to quit, or who are not motivated to quit, to address their nicotine addiction without many of the harms associated with the combustion process. ENDS use in the U.S. has increased dramatically over the past several years, and in 2014, approximately 20.3% of current cigarette smokers reported using e-cigarettes.[3] Among those who had tried to quit smoking in the past year, more than half reported using an e-cigarette to help them quit.[3] Given this increasing use and potential appeal of ENDS among current smokers, there is an imperative need to understand better its potential benefits or harms. However, research to date has been limited by the large variety of ENDS products and the lack of comparability across studies. With the advent of a

SREC, we can now better address several critical questions about potential benefits for smokers who switch to an e-cigarette.

ENDS attempt to duplicate the sensory and behavioral characteristics of cigarettes. Users inhale a nicotine-containing vapor that is partially absorbed through the pulmonary system. Although nicotine itself presents little cardiovascular risk and is not a carcinogen[7], other ingredients besides nicotine are inhaled, and there is the possibility of harm from some of these ingredients. E-cigarette vapor contains particular matter, but the level of toxicity and health effects from these particulates is not yet clear.[8] Frequent exposure to fine and ultrafine particles from tobacco smoke can contribute to pulmonary and inflammatory processes, which in turn, can increase the risk for cardiovascular and respiratory diseases.[9-12] It is not yet known definitely whether the particles delivered by e-cigarettes have the same health effects as the particles generated by conventional cigarette smoke,[8] and there is some suggestion that the amount of particle matter may vary by nicotine content.[13] Some researchers have estimated that e-cigarette aerosol would result in only about 25% of particles being deposited into the circulatory system and organs,[14] far lower than that of conventional cigarette smoking. E-cigarette aerosol may also contain a variety of metals (e.g., tin, nickel, lead, copper, chromium), some of which may come from the heating elements, and which could also be deposited in the lungs and cause respiratory toxity.[8] Overall, though, the evidence to date suggests that although e-cigarette aerosol may contain some toxicants, these are at markedly lower levels than found with tobacco smoke, and that there are negligible levels of carcinogens.[17]

Only a few studies have examined the health effects of exposure to e-cigarette aerosol, and the biological effects are mixed.[8] Some studies, for example, have found that acute puffing on e-cigarettes does not affect pulmonary function [15,16] or inflammatory markers[16], but that it may constrict airways.[15] Most studies of the health effects of e-cigarettes have assessed acute or very short-term exposure effects with relatively small sample sizes, and there is extremely limited data on health effects assessed from e-cigarettes as they are actually used. E-cigarette aerosol may have biological effects, but we need to know more about these effects as smokers actually use the products and whether there are reductions in harm relative to smokers' use of conventional cigarettes. In a recent review of the safety of e-cigarettes, Farsalinos and Polosa[18] concluded that the clinical studies that have evaluated the effects of short-term e-cigarette use on cardiovascular and respiratory functional outcomes have shown that even if some harmful effects are reported, these effects are significantly milder than those derived from smoking conventional cigarettes. Dinakar and O'Connor[19] reached a similar conclusion and further noted that the diversity of e-cigarette products has made it challenging to reach consensus about their safety and efficacy. For example, the sudden outbreak of pulmonary illnesses in Fall 2019 that are known as e-cigarette or vaping associated lung injuries (EVALI) appears to be associated with vaping e-liquids that contain THC, and/or using devices or liquids that were purchased or mixed off market (e.g., off the streets or from friends and family, not from licensed retailors)[63]. The SREC device used in this study does not contain THC and comes from a NIDA-funded SBIR contract for a standardized e-cigarette to NJOY LLC (a requirement for grants funded under this Program Announcement).

2.1. E-cigarettes and Smoking Reduction and Cessation

Currently there is little consensus about whether e-cigarettes aid in smoking cessation or reduction. Several studies have found reductions in cigarettes per day among adult smokers who use e-cigarettes.[20-22] The value of the reduction is likely to depend, though, on the level achieved and perhaps whether it represents a path to cessation, given that reducing the number of cigarettes smoked per day will have smaller health benefits than quitting completely.[1] For cardiovascular disease, even very light smoking (less than 5 cigarettes/day) is associated with a notable increase in risk for disease.[23] A recent systematic review and meta-analysis by Kalkhoran and Glantz [24] concluded that e-cigarettes were associated with less quitting among current smokers. However, there have been substantial criticisms about the methods of this review and inclusion criteria.[25] Another recent comprehensive systematic review concluded that a majority of studies show a positive association between e-cigarette use and smoking cessation.[26] These authors also note, though, that this research is still in its infancy, with few well-designed studies, and at this point, there is not a strong body of evidence to draw any firm conclusions. Malas et al.[26] further conclude that we need randomized controlled clinical trials outside of lab settings and that can provide insight into contextual and behavioral mechanisms. They also note that the effectiveness of e-cigarettes to "reduce withdrawal symptoms and cravings in real-life settings remains uncertain" (p.9).

2.2. Ecological Momentary Assessments (EMA)

EMA provides an excellent window into the lives of tobacco users and a way to examine specific hypotheses about subjective experiences with combustibles and e-cigarettes, and the moderating effects of contexts. It is an excellent vehicle to address the questions about contextual and behavioral mechanisms that Malas et al.[26] suggest are needed. EMA involves repeated sampling of individuals' behavior and experiences in real time in the natural environments in which they occur. EMA maximizes ecological validity, minimizes recall bias, and allows for examining micro-contexts that influence behavior.[27] EMA captures subtle variations in mood as they occur and can do so more accurately than other measurement modalities.[27]

EMA has many advantages over other methods for examining subjective experiences and other influences on tobacco use behaviors. First, EMA is well suited for measuring intra-individual variability and small shifts in mood that may play a role in cueing the use of cigarettes or e-cigarettes. In addition, with the use of random assessments independent from the occurrence of specific events, EMA provides useful comparison information about background moods, urges, and withdrawal symptoms. Second, EMA data allow us to separate between-subject vs. within-subject effects. We have described mixed model approaches incorporating a log-linear structure for determinants of within-subject variances using EMA data[28-30] and have extended this approach to modeling between-subject variances.[31] As illustrated by Hedeker et al.,[31] these approaches are useful in the simultaneous consideration of both between- and within-subject effects. These models allow for the simultaneous testing of hypotheses about whether subjective responses to tobacco use vary by smoking pattern or level (between-subjects effect), as well as whether mood varies with combustible and ENDS use (within-subjects effect). Third, EMA provides the opportunity to examine individual variability (variance) that may enhance our ability to predict changes in tobacco use patterns above and beyond mean information alone. Our work has shown the feasibility of EMA for examining moods, tobacco use, and contexts among adolescents, young adults, and dual-using smokers (those who use both cigarettes and ENDS).

3.0. Objectives/Aims

This project will use EMA to gather real-time reports of smokers' use and experience of SREC as they switch from combustible cigarettes to SREC. We will examine how the proximal contexts and subjective experiences of SREC use differ from smokers' patterns and responses to usual cigarette use, and how these patterns predict switching success. We will examine whether increasing flavor choice will improve adherence to e-cigarettes and so increase the degree of switching. We will assess in real time, smokers' reports of urges and withdrawal symptoms as they switch to SREC. We will also evaluate changes in health and biomarker variables. We will enroll a sample of 120 adult (age 21 and older) cigarette smokers who are interested in reducing their cigarette use by switching to e-cigarettes. Participants will complete baseline assessments and a one-week EMA wave while they are smoking their usual cigarettes, and then will be randomized in a 1:1 ratio to either their usual flavor SREC pods or free choice of flavored SREC pods. Participants in the usual flavor condition will receive either tobacco (regular smokers) or menthol (menthol smokers) while those in the free choice condition can choose from the following SREC flavors: tobacco, menthol, watermelon, and blueberry. Participants in the flavor choice condition will be able to select from these flavors throughout the trial based on their preference. All participants will receive brief behavioral counseling about reducing their cigarette use and switching to the SREC. After an initial week of using SREC, they will complete another EMA week assessing patterns and responses to use of products. Participants will receive 12 weeks of SREC pods; complete daily reports of product use along with bi-weekly check-ins through the end of the 12-week trial, and then complete a one-month follow-up. The total study duration for participants is 18 weeks. **We will address the following specific aims:**

AIM 1: Examine whether conventional cigarette smokers can significantly reduce their combustible cigarette use by switching to SREC. We hypothesize that smokers randomized to the flavor choice condition will show significantly greater reductions in combustible cigarette use than smokers in the usual flavor condition. We will assess changes in use of products over a 12-week trial. We will also examine moderators of effects, including sex, baseline menthol cigarette use (not SREC flavor), and nicotine dependence level at baseline.

AIM 2: Examine whether reductions in conventional cigarette use and uptake of SREC are associated with changes in health and biomarker variables. We will have longitudinal measures of all

combustible tobacco products as well as SREC use and will examine how these longitudinal changes in patterns of use are associated with changes in expired air carbon monoxide (CO); blood pressure; heart rate; weight; respiratory symptoms; withdrawal symptoms; and nicotine dependence. We hypothesize that smokers who show more complete substitution will show greater reductions in CO and respiratory symptoms.

AIM 3: Examine smokers' subjective responses to SREC in real time, as they are used, and whether these responses are associated with cigarette reduction. We hypothesize that smokers in the flavor choice condition will show more adherence to the switching intervention and report higher levels of satisfaction, pleasure, and mood enhancements than smokers in the usual flavor EC condition and that these responses will predict level of cigarette reduction. Data will come from EMA measures and daily surveys. We will also descriptively examine how SREC flavor may be associated with subjective responses.

AIM 4: Examine how patterns of use (e.g., contexts, timing) and subjective experience with SREC differ from conventional cigarette use, and whether differences are associated with success in switching to SREC. These within-subject analyses will use EMA data. We hypothesize that subjects who have fewer differences in patterns and experiences between cigarettes and SREC will reduce cigarettes more and maintain SREC use longer.

4.0 Eligibility

We plan to enroll 120 adult (age 21 and over) conventional cigarette smokers from the Chicago metro area to participate in this study. The eligibility criteria will be assessed via an online screening survey, a follow-up screening phone call with project staff, and an in-person assessment prior to enrollment. Recruitment materials will direct potential participants to a website to complete an online survey to determine initial eligibility. Following this initial screening, we will call potential participants to describe the study requirements, re-assess key eligibility criteria, and schedule the enrollment/baseline visit for those who remain interested. Finally, at the enrollment/ baseline visit, participants must have an expired CO level of 3 ppm or greater and a negative pregnancy test (for female participants of childbearing age, 55 years old or younger) to proceed with enrollment into the study.

Study staff will review responses to the online screening surveys and conduct the phone follow-up calls as well as administer the expired CO test and record the result from the urine pregnancy test (where applicable) to determine eligibility. All screening data will be recorded in a REDCap database and will be reviewed and approved by Co-I, Dr. Diviak.

5.0 Inclusion Criteria

Inclusion criteria are: 1) men and women 21 years of age or older; 2) daily smoking rate of 3 cigarettes/day or greater for at least one year; 3) interested in reducing cigarette use; 4) willing to try e-cigarettes; 5) able to attend in-person assessments at our research office over a 14 week time period; 6) able to read and speak English; 7) agree to use an approved form of birth control during the study (if female and of childbearing age); 8) agree to refrain from using any other vaping or e-cigarette products and devices for the 12-week treatment period; 9) agree to not modify the SREC device and pods in any way; and 10) an expired CO level of 3 ppm or greater (assessed in-person at the enrollment/ baseline visit). A prospective participant's ability to speak English will be assessed directly via the online screening survey as well as their ability to communicate during the telephone screening call, and the ability to read English will be assessed indirectly by comparing responses to the online screener and telephone screener and will be verified during the informed consent process.

4.2 Exclusion Criteria

Exclusion criteria are: 1) current use of any smoking cessation medication or participation in a smoking cessation program or study; 2) current daily ENDS user; 3) currently breast feeding, pregnant, or trying to get pregnant (if female); 4) known allergy to propylene glycol or vegetable glycerin; 5) diagnosed with previous or current EVALI; 6) uncontrolled hypertension and/or, severe mental health problems; 7) current respiratory health conditions (e.g., asthma, COPD); and 8) no two members of the same household may participate in this study. Potential participants who respond inconsistently to the same questions on their cigarette and e-

cigarette use during the screening process will also be excluded. Individuals who are unable/unwilling to carry and interact with the EMA device during two weeks of their first month in the study will also be excluded.

5.0 Subject Enrollment

UIC Recruitment. We will inform potential participants about the research study via study flyers posted in a variety of locations in the Chicago area (e.g., coffee shops, laundromats, convenience stores); Chicago-based newspapers (including alternative newspapers or entertainment publications such as the Chicago Reader and the RedEye Chicago); social media (e.g., Facebook, Twitter, or Google ads); and an email shared via an electronic listserv to the broader UIC community (which includes all faculty, students, and staff). In addition, we may recruit smokers through research registries (UI Health Research Registry, The New Normal), and the extensive University of Illinois (UI) Health network and clinics via flyers posted in waiting areas and placed on reception area/sign-in counters.

All recruitment materials will direct potential participants to a website to complete a web-based screening survey in REDCap. The materials also include the study phone number so that potential participants can speak to a study staff member if they have questions about the research study prior to completing the online survey. Study staff will review responses to the online screening survey in order to determine initial eligibility. Following this initial web-based screening, study staff will call the potential participants who are eligible based on their initial responses and describe the study requirements in greater detail, re-assess key eligibility criteria, and schedule the enrollment/baseline visit for those who remain eligible and interested. The final eligibility assessment occurs during the enrollment study visit where potential participants complete an expired CO assessment and complete a pregnancy test (if female). If eligible after these processes, they begin the consent process with study staff.

Potential participants who are not eligible at screening are informed by email (after the online survey and/or phone screening survey), phone call, or in-person (after the CO assessment and pregnancy test) based on where in the screening process they were excluded. The responses ineligible individuals provided to the screening questions will be maintained as part of the dataset in order to accurately report recruitment and enrollment summaries; however, all identifiable information (e.g., names, phone number, email address, etc.) provided by ineligible individuals will be deleted from all study records at the end of the 1-year recruitment period. The data that remains will only be associated with a study ID. We plan to maintain the contact information during the recruitment period in order to mark ineligible individuals who complete multiple online screening surveys in an effort to enroll in the study despite an initial determination that they were ineligible.

We ensure that our recruitment methods minimize coercion in several ways. First, throughout the screening process potential participants are repeatedly informed that the decision whether or not to participate in the study is entirely their own. We provide detailed study information at all three screening points (online, phone, and during the consent process) to ensure potential participants have a full and complete understanding of what participation in the study involves and let them know that no one will be upset if they decide not to participate in the study. During the consent process we also provide participants with other alternate treatment options for reducing their smoking or helping them to quit, including several other no-cost options (e.g., Illinois Tobacco Quit Line, American Lung Association's online stop smoking link). For our recruitment in UI health clinics, UI clinical staff are not involved in the study in any way. The only involvement is that flyers and handouts about the research study will be available in the clinics. UI Health patient participation in any part of the study (screening through follow-up) is not part of their medical record. We will never share with UI Health clinic staff whether or not their patients completed a screening survey, if they were eligible, or if they enrolled in the study. None of the research staff involved in this study have clinical responsibilities at UI Health.

Trialfacts Recruitment. Trialfacts is a research study recruitment service to which the general population can voluntarily subscribe to receive email notifications about research participation opportunities. When individuals subscribe, they agree to be contacted for future research study opportunities. This study will be listed on the Trialfacts website so that individuals can search studies to identify those for which they may be interested or eligible (similar to the UI Health Research Registry). Trialfacts will also post approved recruitment content on social media. Potential participants who are recruited though Trialfacts will complete the web-based screening survey with Trialfacts. Trialfacts will share the online screening responses of the potentially eligible

respondents with UIC study staff via UIC's installation of REDCap. Once the data is shared, the remaining screening, eligibility, and enrollment process are the same as described above.

6.0 Study Design and Procedures

All human subjects research will be conducted at the Institute for Health Research and Policy at UIC. Some portions of the data analyses conducted by Co-I Dr. Hedeker may take place at the University of Chicago. Dr. Hedeker's role involves guiding the data analyses and writing up results for presentation and publication. Dr. Hedeker will only have access to a deidentified dataset and will not have any responsibility for recruitment, enrollment, consent, or data collection, and will never be able to access any participant contact information.

Design Overview. Participants will complete baseline assessments and a one-week EMA wave while they continue their usual pattern of cigarette use. After their first EMA week, participants will be randomized (within sex) in a 1:1 ratio to receive either SREC pods in their usual flavor (n=60) or pods in their choice of flavor (n=60). Participants assigned to the flavor choice condition can select from the four available SREC flavors (tobacco, menthol, watermelon, and blueberry) based on their preference and satisfaction with the flavor throughout the trial. All participants will receive brief behavioral counseling about reducing their cigarette use and switching to the SREC. After an initial week of using SREC and reducing the number of cigarettes smoked, participants will complete another EMA week assessing patterns and responses to use of both products. Participants will receive 12 weeks of SREC pods; complete daily reports of product use along with bi-weekly check-ins through the end of the 12-week trial, and then complete a one-month follow-up. Female participants of childbearing age (55 years old and younger) will provide urine for a required pregnancy test every 5 to 6 weeks and will be removed from the study if the test indicates a pregnancy. The total study duration for participants is 18 weeks. Table 1 shows the timeline of assessments, procedures, and modality.

Table 1: Timeline of Assessments and Procedures

Week	Procedures	Modality	Visit Duration (in minutes)
0	Screening eligibility	On-line and phone	
1	CO; pregnancy test; baseline questionnaires on tablet (if not already completed); vital signs; height and weight; EMA training; go home with EMA and smoke usual cigarettes	In-person visit	90-120
2	De-brief EMA; CO; Counseling about reduction and switch; brief questionnaire; given week supply of SREC; daily reports of use	In-person visit; daily text/web reports of use	60
3	Return used pods; CO; Brief counseling to problem solve reduction and switch; given new week supply of SREC; start EMA	In-person visit; daily text/web reports	40
4	Debrief EMA week; return used pods; CO; brief review of progress and problem-solve; given 2-week supply of SREC	In-person visit; daily text/web reports of use	40
5	Daily reports of use via text/web	Daily Text/web reports of use	
6	Brief check-in to give next 2-week supply of SREC; return used pods; CO; continue daily reports of use via text/web; pregnancy test	In-person visit; daily text/web reports of use	20
7	Daily reports of use via text/web	Daily Text/web reports of use	
8	Brief check-in to return used pods; given next 2-week SREC supply; CO; continue daily reports of use via text/web	In-person visit; daily text/web reports of use	20
9	Daily reports of use via text/web	Daily Text/web reports of use	
10	Daily reports of use via text/web	Daily text/web reports of use	
11	Brief check-in to return used pods; CO; given next supply of SREC; continue daily reports of use via text/web; pregnancy test	In-person visit; daily Text/web reports of use	20
12	Daily reports of use via text/web	Daily text/web reports of use	
13	Daily reports of use via text/web	Daily Text/web reports of use	
14	End-of-treatment full assessment battery; CO; vitals; height and weight; collect SREC device and remaining pods; daily reports of use surveys end	In-person	60
18	Brief follow-up about cigarette and ENDS use over past month	Web/phone based	15

Baseline/Enrollment Visit Week 1. The first visit begins with the final set of screening assessments: CO > 3ppm and negative pregnancy test for female participants. Once the screening is complete, participants who remain eligible will start the consent process. Staff describe the study, answer all questions, ensure understanding of the study information, and re-assess interest in participating. Participants who remain interested will be asked to sign the informed consent form. Participants will complete the baseline questionnaire on a tablet, and participants will have vital signs taken (blood pressure, heart rate, height, weight). Participants will also be trained on the EMA protocol (see below for more details) and given instructions to go home and smoke as they usually do. **The purpose of this first EMA week is to provide baseline data about the participant's smoking pattern which will be compared to their SREC/cigarette use pattern after switching.**

Week 2 Visit. Participants will complete a brief questionnaire and complete an expired CO assessment. Study staff conduct a debriefing interview to review the EMA week and their compliance with the protocol. Participants will be randomly assigned to the two flavor conditions, stratifying for gender. Those participants assigned to the choice condition will select from four SREC flavors (tobacco, menthol, watermelon, and blueberry) based on their preference. Participants assigned to the usual flavor condition will receive tobacco pods if they smoke regular cigarettes and menthol pods if they smoke menthol cigarettes. Participants in both conditions will receive **brief behavioral counseling** (see below for more details) on reducing their combustible cigarette use and using SREC as a substitution for cigarettes. Starting this week, participants begin to receive daily email or text prompts (based on participant's preferred mode of communication) to complete a brief online survey on their use of cigarettes, SREC, and non-SREC e-cigarette use each day.

Week 3 Visit. Participants will bring back all used and unused pods for adherence counts, complete a brief questionnaire about subjective reactions and potential adverse effects from SREC, and complete the CO assessment. Study staff review their progress with reducing their smoking and switching to SREC and continue brief behavioral counseling about reducing smoking and substituting SREC. Participants will be told that their goal is to completely switch. Participants will receive feedback on their compliance with the first EMA week and additional training to ensure accurate reporting of both SREC and cigarettes on the app. Participants go home with another week supply of SREC, begin the second 7-day EMA wave, and continue completing daily reports.

Week 4 Visit. Similar to the week 3 visit, except that participants will again debrief their EMA week for compliance and problems; complete assessments; and review their progress with switching to SREC. Participants will receive a 2-week supply of SREC and continue completing daily reports.

Weeks 5-13. Participants will return to the study office every 2 to 3 weeks to return pods, receive a new supply, and complete CO assessments. During the week, they will continue completing daily reports. Additionally, female participants of childbearing age will provide a urine sample every 5 to 6 weeks; those with positive test results (a result indicating pregnancy) will be removed from the study.

Week 14 (End-of-Treatment). Participants return to the study office to complete a full assessment battery and return the SREC device and all pods. They will be encouraged to continue to stay off/reduce all combustible cigarettes but will not receive any more study provided SREC pods.

Week 18 (One Month Follow-up). Participants will receive an email or text prompt to complete a brief web-based survey (phone if needed) about their cigarette and ENDS use during the past month as well as motivation and confidence to continue to stay off combustible/use ENDS in the future.

All study procedures are being done for research purposes; none are part of their health services or care.

6.1. Behavioral Intervention

Participants in both conditions will receive brief behavioral counseling on several cigarette reduction strategies, including substitution of cigarettes with the SREC. Participants will be told to carry the SREC with them as they would their cigarettes, and to use the SREC when they feel the urge to smoke. Participants will

be told that it may take a few days to adjust to the SREC and a pattern of use, but that each day they should try to reduce the number of cigarettes smoked. Once participants have a week of experience with the SREC, they will be encouraged not to carry their usual cigarettes with them as another strategy of reducing their cigarette use. Staff will work with participants to set individual goals for reduction during this first week, with the goal of achieving at least 75% reduction in the number of combustible cigarettes smoked by the end of the week, and all encouraged to reduce further. Participants will be told that they should strive for complete switching after the first week. Participants will also be told not to use any other tobacco or nicotine products during their participation in the study.

The behavioral intervention is based on Dr. Mermestein's prior work on a recently completed clinical trial evaluating treatment components to help smokers who were unmotivated to quit, to reduce and to attempt to quit. This treatment included a behavioral reduction component, which focused on strategies to help smokers systematically cut down on cigarettes. We are adapting this brief behavioral intervention by also providing coaching on how to use the SREC as a replacement for some cigarettes throughout the day.

Fidelity and staff competence at providing the intervention will be measured, assured, and maintained throughout the study in multiple ways. First, standardized training on delivering the intervention will be provided by Drs. Mermelstein and Diviak. Training will involve 40 hours (some self-study and review; others in-person, both individual and group learning activities). Training will include both didactic presentations and role-playing scenarios. Second, we will implement a tiered program of evaluating competence in delivering the intervention. Individual role-play sessions will be evaluated by Dr. Diviak for adherence and skillfulness. Once staff role-play meets performance criteria, staff will be certified for observed participant visits. Participant visits will be observed and evaluated by Dr. Diviak until staff independence is certified. Third, all staff will attend weekly group supervision with Drs. Mermelstein and Diviak to discuss cases, concerns, and challenges. Fourth, at the end of each study visit containing treatment delivery, study coaches will complete a self-assessment checklist of critical intervention behaviors and materials delivered and document the duration of the study visit. These records, stored in REDCap, will be subject to periodic review. Finally, 10% of all staff's treatment visits will be observed by Dr. Diviak throughout the study and evaluated for protocol adherence using a standardized rating scale. Coaching staff with scores falling below 85% of the adherence standard will receive additional supervision, observation, and feedback. If adherence falls below 75%, the coach must complete "booster" training and be recertified in role-playing before resuming interactions with intervention participants.

Some participants may decide that they want to quit smoking altogether during their study involvement. We will support their quit efforts by adapting the behavioral intervention strategies from cutting down to quitting. This will include coping with urges and cravings, preparing for high-risk situations (i.e., situations that are likely to trigger urges to smoke), and encouraging social support. Health coaches will ask participants their preference on continuing to use the SREC during their quit attempt. We will honor participant preference and stop or continue dispensing additional SREC pods during their quit attempt.

6.2. SREC Intervention

The SREC device to be used in this study comes from a NIDA-funded SBIR contract for a standardized e-cigarette to NJOY LLC (a requirement for all grants funded under this Program Announcement). The SREC system consists of the SREC Device and the SREC Pods. The device is rechargeable via USB connection, and it measures 88 mm in length, 30mm in width, and 13 mm in depth/thickness. The device weights 54 +/- 5g and the Filled Pod weights 7.5g +/- 0.5g. The SREC Device contains a rechargeable 400 mAh lithium-ion battery cell to deliver power to the SREC Pods and the settings cannot be adjusted by the user. The SREC packaging pouch for each pod will be labeled "For Investigational Use Only." The SREC Pods will be tobacco, menthol, blueberry, or watermelon-flavored 1.9mL e-liquid in sealed disposable containers with 5% nicotine. SREC Pods have 0.3 mg/55mL of nicotine and deliver 55 mL puffs with about 300 puffs per pod. NJOY SREC has a Tobacco Product Master File on file with the Center for Tobacco Products (CTP) at the FDA with complete technical characteristics of the device, pod, and e-liquid as well as the SREC nicotine pharmacokinetic delivery and profile.

The 12-week SREC trial provides an adequate time for participants to adjust to the SREC (there is often a learning curve with using e-cigarettes) as well as to evaluate whether they can sustain a switch. We also based the duration of treatment on the frequent length of NRT trials (e.g., nicotine patch, gum, etc.). The SREC Pods are packaged two to a pack. At study visit 2, when the SREC is first given to the participant, study

staff will dispense fours packs (8 pods) to each participant. Participants in the flavor choice condition can select the SREC flavor(s) based on their personal preference. Some participants may select only one flavor and others may want to try one of each during this week. All flavor selections are carefully tracked in the project database. During this week, participants will start experimenting with the smoking reduction strategies and with using the SREC with a goal to reduce their cigarette smoking by 75% by the end of that week. One pod a day should be sufficient for this initial week. Over time as participants get experience with the SREC and reducing their smoking, they can make decisions about how much, if any, use of SREC they prefer. We can adapt the number of pods dispensed at each visit based on their success with reduction and their level of SREC use. At each visit, study staff will review their use of cigarettes and SREC since the previous visit and make a decision with the participant about the amount of product they feel they need before their next study visit. For participants who smoke 20 cigarettes or less a day, the upper limit for SREC distribution will be one pod per day. For participants who smoke 21 or more cigarettes a day the upper limit for SREC distribution will be two pods a day. Additionally, at each visit, participants in the flavor choice condition will continue to select the flavor from the four options based on personal preference and success with reduction. Study staff may encourage participants to try other flavors if they are struggling to reduce their cigarettes, but otherwise will not direct or suggest flavors to the participants.

Use of SREC and compliance with substituting SREC for cigarettes will be assessed via self-report and by return of all SREC pods that have been distributed at each study visit. All the open, returned pods will be weighed. Study staff will track the number and flavor of SREC pods dispensed to the participant at each visit. Participants will be instructed to return for their next study visit with all of these pods, regardless of whether they are empty or not. Participants will earn $20 at each of these visits if they return ALL the pods they were given at the previous visit. Compliance with SREC is also assessed via self-report of use on the daily use surveys (week 2 through week 14) as well as at each of the study visits at weeks 3, 4, 6, 8, 11, and 14.

We will monitor both SREC (and any other e-cigarette use) and cigarette use throughout the study in order to ensure that participants are not creating a pattern of increased product use over an extended period of time. However, in the early stages of using SREC, an increase in nicotine exposure may occur as participants experiment with using the new device and practice the strategies from the behavioral intervention. As they learn which cigarette reduction strategies work and which do not, and assess their responses to the SREC (e.g., do they like the taste, is it pleasurable, does it reduce any urges or cravings for a cigarette), a temporary increase in use and exposure to nicotine is neither unexpected nor worrisome. Participants will be informed during the consent process and again during health coaching that over time if they use the SREC without reducing the amount of cigarettes they smoke they may increase their overall nicotine exposure which may increase withdrawal symptoms if they decide to quit. We will limit the amount of SREC dispensed as noted previously to limit the extent to which participants can increase their nicotine exposure. Nicotine exposure is difficult to assess from simple measures of product use. The amount of nicotine a person is exposed to is influenced by a number of factors beyond the amount of cigarettes and e-cigarettes used per day. Race, gender, nicotine metabolism, the level of nicotine dependence, the way in which a smoker smokes the cigarette (puff duration, volume, velocity and inter-puff intervals), the amount of nicotine present in the cigarette, and the presence of menthol in the cigarette all influence a given smokers nicotine exposure. Health coaches will track the amount of product use (both cigarettes, SREC, and any other e-cigarettes) throughout the study and will provide feedback to participants if they are only increasing their use of SREC without decreasing cigarettes. Starting with the week 2 visit, the coaching discussions are focused on developing strategies for decreasing their cigarette use and problem-solving how to manage any difficulties associated with this process. Health coaches will also provide feedback based on the Adverse Event reports provided at each study visit, particularly those that are associated with over exposure to nicotine. We have an upper limit on the number of pods that will be dispensed at each visit to limit the amount of study provided nicotine. Finally, the study PI, study medical monitor, or the DSMB can decide to stop dispensing SREC pods to participants if their use or adverse events warrants; the DSMB will review reports quarterly during the intervention period but will also hold phone and web meetings as needed to review problematic adverse event cases.

We will store the SREC device and all pods in a locked cabinet in a locked room which only study staff who interact with participants can access. The SREC pods are packaged two to a pack and each pack is marked with tracking numbers that will be entered into a spreadsheet when distributed to participants.

Possible side effects of using e-cigarettes, whether the SREC or any other ENDS, include throat irritation, dry cough, mouth irritation, nausea, headaches, and dizziness. Less frequently reported side effects include: sore throat, dry mouth, shortness of breath, and mouth ulcers. Overuse of any product containing nicotine (or using multiple nicotine containing products) may increase the risk of nicotine toxicity. Although the use of SREC along with cigarettes in a research study warrants caution and careful monitoring, it is important to note that studies conducted to date with dual users of cigarettes and ENDS products demonstrate that using both products appear to be safe with few problems of nicotine toxicity. Symptoms of nicotine toxicity include pallor (pale appearance), cold sweat, nausea, excessive salivation, vomiting, diarrhea, tremor, mental confusion, and overall weakness. The likelihood that participants would continue using SREC and smoking cigarettes at levels that would cause problems is small; however, we will assess symptoms of nicotine toxicity at every study visit and will take all necessary steps to minimize any risks associated with using the SREC while continuing to smoke. Study staff will provide an information sheet and instruct participants how to identify symptoms of nicotine toxicity, and to reduce their cigarette smoking and use of SREC to avoid them. If needed, study staff will limit the distribution of SREC pods and consult the study safety monitor, Dr. Jon Klein, to determine next steps (see below).

Finally, another possible side effect of regular e-cigarette use is developing an EVALI; however, the likelihood of developing an EVALI while using the SREC is minimal. According to the CDC's recent investigation, EVALI cases were associated with vaping THC and using products purchased from non-licensed vendors (e.g., off the street, from friends or family)[63]. In order to minimize the risk of developing an EVALI, enrolled participants must agree to use only the study provided SREC products and to not modify the device or e-liquid in any way. Study staff will provide participants with information and guidance on EVALI from the CDC and instruct participants how to identify the early signs and symptoms of an EVALI. Symptoms reported from the recent EVALI outbreak include: respiratory symptoms, including cough, shortness of breath, or chest pain; gastrointestinal symptoms, including nausea, vomiting, stomach pain, or diarrhea; and nonspecific constitutional symptoms, like fever, chills, or weight loss[63]. Additionally, study staff will assess presence and severity of symptoms associated with EVALI along with any e-cigarette products used (SREC or non-SREC) at each study visit and include this information with any potential AE or SAE reporting.

At each study visit following week 2, adverse events (AE) and unexpected problems (UPs) with the SREC are collected using a standardized AE Patient Query Form adapted from Dr. Mermelstein's prior research studies using NRT while reducing cigarettes. This form is stored in a REDCap database. AEs discovered outside of study visits, such as through a phone call or other administrative contact (e.g., appointment reminder or rescheduling calls), will also be documented using the standardized AE form and followed up with to assure participant safety. Clinical staff interviewers are the first line of staff to monitor and assess AEs and UPs. Staff are instructed to notify Drs. Diviak and Mermelstein of these events so that a plan to can be put into place and appropriately monitored. However, Drs. Mermelstein and Diviak will also receive an automatic notification from REDCap upon submission of every AE report in order to trigger a review. The study safety monitor (Dr. Klein) will review, adjudicate, and document decisions or request that additional details be gathered from the participant, all within the secure UIC REDCap web portal. Using this system, real-time AE reports can be generated at any time for the DSMB, UIC IRB, and/or NIDA, for both regularly scheduled reviews as well as in the event of any SAEs requiring expedited reviews. SAEs will be immediately reported to the medical monitor, Dr. Klein and to the IRB. Dr. Klein will address these with the participant to ensure that the participant is linked with appropriate follow-up medical care.

6.3. Surveys

We will collect data via several different processes: 1) Online/In-person assessments (questionnaires and physiological markers; vital signs); 2) Automated email prompts providing web or text-based links for participants to report cigarette and SREC use at the end of each day; 3) EMA app during two separate 7-day periods (weeks 1 and 3); and 4) web or phone-based questionnaire for the one-month follow-up. All participants in both conditions receive all assessments.

Table 2 presents the timeline of the constructs assessed. Proposed measures for the questionnaires are based on established scales/measures and were selected to harmonize with ongoing national surveys (e.g., PATH- Population Assessment of Population and Health Study). All measures will be ones with good

psychometric properties and that we have used in prior research and may be modified based on need to harmonize with other SREC studies.

Table 2: Assessments	**Week Number**														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**18**
Demographics	x														
Medical History/Perceived Health	x														
Respiratory Symptom Q's (SGRQ)[42]	x													x	x
Body Weight and Height	x													x	
Vital Signs: e.g., BP, heart rate	x	x	x	X		x		x			x			x	
Smoking and total tobacco use history (all forms combustible and non); patterns and quit attempts; prior cessation medication use	x														
Nicotine dependence: FTND[43], WISDM[44]	x													x	
Breath CO	x	x	x	X		x		x			x			x	
Pregnancy test (female only)	x					x					x				
Withdrawal symptoms (Minnesota Nicotine Withdrawal Scale; Wisconsin Withdrawal Scale[45])	x	x	x	X		x		x			x			x	x
Craving and urges (QSU-brief)[46, 47]	x	x	x	X		x		x			x			x	
Satisfaction/Pleasure with cigarettes/e-cigs; Subjective experience; appeal [48,49]	x	x	x	X		x		x			x			x	
Motivation to reduce and to quit smoking (rating scale)	x													x	x
Motivations to use E-cigs	x													x	
E-cig Expectancies	x													x	
Intentions to use E-cigs	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x
Confidence to reduce cigarettes and quit (rating scale)	x													x	
Tobacco use in social network/household	x													x	
Social support for reduction/quitting	x													x	
Mood: PANAS[50]	x													x	
Alcohol, Marijuana and Substance Use	x													x	
Adherence/Use of SREC			x	X	x	x	x	x	x	x	x	x	x	x	
Daily Use of Cigarettes/SREC	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (e.g., throat irritation, nausea)			x	X	x	x	x	x	x	x	x	x	x	x	

A. A **Comprehensive questionnaire** (baseline and 14-Week End of Treatment visits) will be completed in-person to assess key constructs [e.g., sociodemographics, tobacco and nicotine use (history, dependence, attitudes, motivations, intentions, perceived harm), tobacco environment, cessation history and intentions, and other substance use]. Each questionnaire will take approximately 30 - 40 minutes to complete. Shorter **brief surveys** (5-7 minutes to complete) will be completed at weeks 2, 3, 4, 6, 8, and 11. These measures serve as important descriptors of our sample, serve as covariates or moderators in our analyses, and serve as predictors of success in reducing cigarettes and switching to SREC over time.

B. A **daily use survey** completed online via REDCap from an emailed or texted survey link starting at the week 2 visit through the week 14 visit (over the 12 treatment weeks) to assess the use of cigarettes, SREC, and any other e-cigarette/nicotine vaporizer. Each of these surveys will take about 1 minute to complete. This brief survey will serve as an indicator of change in patterns of use as well as a way for the Clinical Interviewer Staff to track progress with cigarette reduction and to monitor nicotine exposure during the treatment phase. Daily surveys ask about the number of cigarettes smoked and the number of SREC or other e-cigarette episodes on the previous day (an episode is defined as 15 puffs or a period lasting about 10 mins). We also ask if the participant finished a pod on the previous day.

C. **Two, week-long waves of EMA data collection** using a **study provided smartphone**, the first wave will take place immediately following completion of the baseline questionnaire (week 1 visit through week 2 visit), and the second wave will take place starting at the week 3 visit through the week 4 visit. The first week of EMA provides the baseline comparison with combustible cigarettes to the second EMA wave when participants will have one week of experience with using the SREC and some practice cutting down on their cigarette smoking. Each EMA wave will cover 7 consecutive days, ensuring both weekday and weekend sampling.

We will provide a study smartphone with the custom app installed to each participant. The app is specifically developed for the EMA data collection, which will conduct brief tobacco use interviews through random prompts and participant-initiated recordings of cigarette/SREC/e-cigarette use episodes. The EMA app will “beep” randomly between 5 -7 times a day during waking hours, and ask questions about the participant's daily experiences, such as what they are doing, who they are with, and how they are feeling. It will also ask about cigarette/SREC/e-cigarette use and use of alcohol and marijuana. These interviews will take about two minutes each to complete. Participants also initiate an interview on the app each time they smoke a cigarette or use the SREC device (or other e-cigarette/vaporizer). Each of these interviews also take about 3 minutes to complete. When participants event-record cigarette/SREC use, they respond to questions about their immediate context and mood, but also answer questions related to their cigarette/SREC use. First, they will indicate which product they are using, and subsequent questions are tailored to that product. They will be asked about quantity (e.g., how many cigarettes, how many puffs), how much they wanted to use that specific product, how strong their urge was to smoke (asked regardless of product used), how much they “craved” a cigarette (asked regardless of product used), and potential withdrawal and nicotine-related symptoms (restless, impatient, hungry, sick, buzzed). They will also be asked about "throat hit" and any throat irritation. Other withdrawal symptoms are already included in our mood assessments (e.g., irritable, trouble concentrating, anxious). We will train participants individually on how to use the app. Given the ubiquity of smartphones, participants rarely have difficulty completing prompts. After the first day, the trainer will call participants to assess compliance and assist with problems. Research staff will be available via phone and email throughout the week to respond to research or technology issues with the phone or app.

D. **Semi-structured, debriefing interview** (see Appendix: ED Debriefing Interview) following each wave of EMA data collection this interview will be conducted to assess compliance with the EMA protocol, reactivity to carrying the ED, a review of data quality, and obtain feedback on the EMA data collection experience. The debriefing interview will take about 20 minutes.

E. **Carbon-monoxide (CO) level** in expired air will be measured using a digital monitor at each study visit allowing us to examine changes in CO over time along with changes in patterns of cigarette and SREC use. There are no required qualifications or credentials for the use of a carbon monoxide (CO) monitor. It is a very basic device that simply requires a subject to exhale into a disposable (single use), mouthpiece attached to the digital monitor. All staff involved in the implementation will be trained in the protocol, which includes the following:

1. A member of the research staff will insert a new mouthpiece, turn the monitor on and hand the monitor to the participant.
2. The participant will be instructed to inhale, hold the breath for 15 seconds, and then exhale the entire breath through the mouthpiece into the digital monitor while following the on-screen prompts.

F. **Urine pregnancy tests** will be administered to female participants of childbearing age (defined as 55 years old and younger) during the Week1/Enrollment visit and every 5 to 6 weeks during the study; those with positive test results (a result indicating pregnancy) will be removed from the study.

G. Other **vital signs** will be measured at study visits including height and weight (baseline and end of treatment), blood pressure and pulse (at every study visit).

6.4. Specimen Collection

Urine test results will be collected from female participants to determine whether or not they are pregnant before study enrollment (Week1) and every 5 to 6 weeks thereafter until study completion. There will be no storage of collected urine. The urine samples and test sticks will be disposed of immediately after a successful pregnancy test has been conducted and recorded by study staff.

7.0 Expected Risks/Benefits

Potential Benefits. Participants will receive brief behavioral counseling and the SREC to help them reduce their combustible tobacco use which has the potential for improvements to their health as well as money saved from purchasing cigarettes. Participants will receive monetary payment for completion of their assessments through a university issued check. Participation in the study ultimately will help other smokers in the future by improving our knowledge of how e-cigarettes might be used to help smokers reduce or stop smoking cigarettes.

Protections Against Risks. We believe that the risk of participation is minimal, and any potential risks from the use of SREC are likely to be considerably less than those that result from cigarette smoking. In general, there have been extremely few documented risks associated with non-THC, nicotine containing e-cigarette use among current smokers. Participants will be informed about EVALI and provided with CDC recommendations on e-cigarette use during the consent process and throughout the trial. Participants will also be informed of potential adverse effects of reducing their smoking and using the SREC, including experiencing withdrawal symptoms. Over the course of our previous research studies, we have developed extensive procedures and protocols for minimizing the risks of participation.

Participant Training for EMA. Clinical Staff conduct careful training procedures with participants at the beginning of each EMA week. This training is focused on appropriate use of the EMA device, including when to "suspend" the EMA program so that it will not randomly prompt participants during times when it might be dangerous to respond to interviews (e.g., driving). In addition, staff will role-play with participants on how to deal with potentially awkward situations in order to complete random prompts or event record their cigarette and SREC use. The trainer will help participants anticipate and problem-solve any concerns they have about using the device in their everyday lives for the 7-day monitoring period.

Distress. We believe the risk of experiencing distress as a direct result of participating in the proposed research is minimal given the nature of the measures that we will be collecting. Participants may experience some withdrawal distress as they switch to SREC and reduce their cigarette smoking, but we believe that this is minimal. In our 20 years of conducting similar studies with a variety of high-risk populations (e.g., adolescents, young adults, disadvantaged) we have not had participant complaints about the procedures causing any distress; rather participants usually find the procedures interesting. However, we are prepared to manage this situation, should it occur. Drs. Mermelstein and Diviak are clinical psychologists and will provide training for staff on identifying and responding to emotional distress in a research participant. Staff will be required to notify Drs. Mermelstein and Diviak immediately upon discovery of any problems or distress with a participant.

Confidentiality. Confidentiality of all data we collect are assured by using a unique numerical identifier for each participant. The master list of name and identifier match is restricted to only personnel who require the match for essential study tasks. The list will reside in a password protected file kept separate from all other data and study materials. Materials that contain individuals' names or other important contact information (e.g., mailing address, phone, email) will also be restricted and password protected. Identifying information and data are not stored together. The EMA program is password protected and accessing and downloading the data requires a custom download program that can only be accessed by authorized study staff. If a participant were to lose a phone, no one else could access data stored by the EMA program. We have developed extensive procedures and protocols in our current and previous EMA studies with no accidental disclosure or adverse consequences to study participants. We believe that staff training is crucial to ensuring confidentiality. Staff will participate in UIC's human subjects protections training, along with specific, project-focused training and frequent reviews with Dr. Diviak and Mr. O'Keefe (Senior Data Manager) to ensure staff understanding and compliance with project protocols.

Risks around the e-cigarette (SREC). We believe that the risks of adult regular smokers using SREC are minimal, given the prevalence of use of e-cigarettes and the consensus that they are far less harmful than conventional cigarettes. According to the recent (2018) National Academy of Science report, "The evidence about harm reduction suggests that across a range of studies and outcomes, e-cigarettes pose less risk to an individual than combustible tobacco cigarettes." (p. S-8). Nevertheless, we will discuss with participants that all tobacco use may present some harm, and that no tobacco use is healthy. We will provide an information sheet to participants each time we dispense the SREC to them. At the enrollment visit (during the consent process) and at the end-of-treatment visit, we will tell participants that the long-term safety and health effects of using e-cigarettes is unknown. We will also discuss in-person and include on the information sheet that the SREC device contains nicotine, which can be hazardous to children and pets if ingested. We plan to discuss plans for storing the device and refills in their homes. We will also provide education to participants on the symptoms of nicotine toxicity (nausea and vomiting) and the signs and symptoms of developing an EVALI so that they are aware and can reduce their exposure if the experience these symptoms. Additionally, the SREC packaging of the battery and each pod is clearly marked “for investigational purposes only.” We also will instruct participants about the risks associated with using nicotine products while pregnant and/or nursing, and study staff will record results from pregnancy tests taken during study visits for women of childbearing age throughout participation.

Given that the risks involved in this proposed research are relatively minimal, the benefits of participating greatly outweigh the risks.

8.0 Data Collection and Management Procedures

The data for this study are provided directly from the participant and are collected solely for research purposes. Data will come from: the online and telephone screening surveys, computer administered questionnaires, online daily use surveys, health assessments (pregnancy test results, expired air CO, height, weight, blood pressure, pulse), semi-structured debriefing interviews, and real-time EMA. Aside from the EMA data collection, all other data will be collected using REDCap and maintained on the secure IHRP server. Participants will complete questionnaires for the in-person visits on a tablet using REDCap to reduce missing data or errors.

The questionnaires completed by participants at all study visits as well as the daily use surveys will be programmed into REDCap (baseline and week 14/End of Treatment) or REDCap (all brief questionnaires at all remaining study visits) for data collection on a tablet during the in-person visits. The daily use surveys will be programmed within REDCap, a secure web-based application for data management that can be programmed for daily email reminders and links.

The health measures (CO, pregnancy test results, height, weight, blood pressure, and pulse) will be recorded on a hard-copy forms that only contains the study ID. This data will be entered into REDCap shortly after each study visit by research staff. The hard copy forms will be filed in a locked cabinet in a locked office until for four years after the study is completed and then shredded.

The EMA data collection (i.e., smartphone and app) will be password protected so only the participant has the ability to enter and record data. All EMA data reside on the app until the participant returns to our study office at the end of their EMA week. We then download the data to our secure server and wipe the app clean of all data. All entries will be time and date stamped, and the app will record response time to a prompt, missed prompts, wake and sleep times, and app “suspensions” and the reasons. Participants may “suspend” the app for up to three hours when responding would be impractical (e.g., while driving; at movies). The app programming prevents skipping items or entering out-of-range values. Once the interviews are recorded, only study personnel with an administrative password will be able to access the data stored on the device, from which it will be downloaded to a laptop for debriefing interview purposes, and then transferred to the secure IHRP server. The laptop used in the debriefing interview will never be connected to the internet and will never leave our research office while there is data on it. Immediately following the debriefing interview, the laptop will be connected to the IHRP server to transfer the data, and then the data will be deleted from the laptop.

Managing EMA data includes data collection, debriefing, documentation, extraction, aggregation, and cleaning. During the EMA week, data are stored on the app on the study-provided smartphone. At post-EMA debriefing at week’s end, we collect the phone, download the data (for storage on a secure server), and print a debriefing report. The report contains all the participant’s interactions with the app, helps gauge compliance,

and establishes positive reinforcement for future waves. The report documents problems encountered (e.g., erroneous entries). These data are corrected after data aggregation. All ASCII files are aggregated using MS-DOS batch commands; the resulting aggregated ASCII is read into SAS and formatted.

Data Management. Mr. O'Keefe will develop the centralized databases that will be used to collect, process, and manage data relating to the eligibility screening, enrollment, randomization, intervention delivery, and follow-up. Data processing will include: de-identification of the online screener and implementation of the unique ID for each participant, and transferring the data from the smartphones to the IHRP secure server, followed by subsequent cleaning, documentation, and construction of master files for all of the data collection instruments. The datafiles will be maintained on the IHRP secure network that allows investigators and key research personnel access to data files and accompanying documentation. These files will be made available to approved investigators on the project.

REDCap has sophisticated user rights controls that allow some users access to certain REDCap functions but not others (e.g., allowing data exports or not, viewing summary statistics and charts, adding or editing records, etc.). It also supports a complex longitudinal study structure to allow for form reuse and a univariate or "stacked" data structure. We will leverage the many built-in features in REDCap (e.g., data type validation, valid values/range rules, required responses) and extensive data rules that allow for complex real-time quality control checks (e.g., of missing values, out of range values, logic comparisons, cross form/event consistency).

Every other week, a quality control report will be generated to quantify the accuracy and timeliness of data collection and entry, identify missing data, and examine frequencies to detect unanticipated problems or biases. Quantitative data stored in REDCap will be exported directly from the REDCap database to the Switch to SREC's storage folder on the IHRP network for processing. Research staff responsible for analyzing data, both at UIC and UofC, will only have access to processed and deidentified data files. They do not have access to raw responses from the REDCap database, nor can they access participant names or other contact information. Data will be shared with Dr. Hedeker at UofC using Virtual Private Network (VPN) access to the IHRP server.

Syntax will be used for constructing the planned dataset and for running all analyses. This will allow the investigators to review each step of the analytic process for errors and to ensure the appropriate analyses have been done (and can be repeated with the same results). These syntax files will be saved along with the output files and each corresponding manuscript so that it can be used in responding to reviewers, and it will be available upon request for sharing.

9.0 Data Analysis

Aim 1. Examine whether conventional cigarette smokers can significantly reduce their combustible cigarette use by switching to SREC. We will have assessments of the amount of SREC and combustible cigarettes used every week for 12 weeks. SREC/e-cigarette use per day is captured by the total number of e-cigarette episodes defined as about 15 puffs or a period lasting about 10 minutes. Both of these outcomes will be modeled as count data (average # cigs/day and SREC episodes/day for each week) using a mixed-effects Poisson regression model (or Negative Binomial model if the Poisson assumption of equality of mean and variance is not met). In these analyses, we will examine primarily linear and curvilinear changes across time using orthogonal polynomial transforms, in order to assess the independent effects of these two types of trends, which will be treated as random effects to allow heterogeneity across subjects in the time trends. These time trend analyses will allow us to investigate the **sustainability of reductions in cigarette use and changes in SREC use.** In addition to the effect(s) of time, the main independent variable is group (usual flavor or flavor choice). Although we expect the group effect to be consistent across the 12 weeks, we will test whether the group effect varies across time (i.e., group by time interaction). For example, it may be likely that differences between the groups increase over time if the usual flavor group more rapidly relapses back to smoking cigarettes and gives up on their SREC. Our primary endpoint will be the model-based estimate of the group difference at the final 12-week timepoint (study week 14). We will also consider the proportion of participants who achieve total abstinence from combustible cigarettes at the end of the12-week trial (defined as no cigarette smoking in the past 7 days and confirmed by CO < 3 ppm; see power section). Although our primary endpoint is the end of the 12 weeks of treatment, (week 14) we will also evaluate effects at the one-month follow-up. In terms of these primary outcomes, we will further examine the degree to which

group differences are moderated by gender, baseline menthol cigarette use (not SREC flavor), and nicotine dependence level, and also examine the degree to which baseline characteristics might predict success on these outcomes. We will use descriptive statistics to report the frequency of flavor choice, how that varies over time, by condition, and by level of reduction.

We will also be weighing all returned SREC pods and will also be able to develop a measure of SREC use per week based on SREC pod weight.

Aim 2. Examine whether reductions in conventional cigarette use and uptake of SREC are associated with changes in health and biomarker variables. Smokers may vary in how completely they substitute SREC for their conventional cigarettes. Thus, for each participant, we will have, on a weekly basis, the number of cigarettes smoked and the number of SREC episodes or returned SREC pod weights. As indicated above, these will be modeled using mixed models for counts, which yield empirical Bayes estimates for each subject of their change across time in cigarette and SREC usage. We will examine how these change in usage estimates are associated with changes in the following variables: 1) CO level; 2) blood pressure; 3) heart rate; 4) weight (assessed baseline and at end); 5) self-report of respiratory symptoms (baseline and at end); and 6) nicotine dependence (assessed at baseline and end). For each of these continuous outcomes, we will use linear mixed models with effects of time and group (usual flavor or free choice), and group by time interaction if significant. To these models, we will add in the empirical Bayes estimates of cigarette and SREC change (obtained from the stage 1 mixed models for counts) and specifically examine the change by time interactions (and change by group by time if the group by time interaction is significant). As the empirical Bayes estimates from the stage 1 analyses have uncertainty attached to them, we will use the resampling approach advocated by Tsonka et al[58] for using empirical Bayes estimates from a first stage analysis as covariates in a second stage model.

Aim 3: Examine smokers' subjective responses to SREC in real time, and whether these responses are associated with cigarette reduction. Levels of satisfaction, pleasure, mood change following use, and withdrawal symptoms will be assessed via EMA during the second week of SREC use. Level of satisfaction, pleasure, and mood will be assessed following each use of SREC (event report), and withdrawal symptoms will be assessed both during random times and following SREC use. We will also descriptively examine how the SREC flavor may be associated with adherence and overall level of subjective responses. We will use linear mixed models to compare groups in terms of the EMA subjective reports and withdrawal symptoms. Also, using the empirical Bayes estimates from these linear mixed models of EMA-reported subjective experience and withdrawal, we will examine whether these predict longitudinal changes in cigarette use over the following weeks, which will be modeled using a Poisson mixed model including effects of group, time (and group by time if significant). We will specifically examine the effects of satisfaction and withdrawal on cigarette use, both as main effects and as interactions with time if significant. Again, we will follow the resampling approach[58] to account for the uncertainty of the empirical Bayes estimates.

Aim 4. Examine how patterns of use (e.g., contexts, timing) and subjective experience with SREC, differ from conventional cigarette use, and whether differences are associated with success in switching to SREC (giving up or reducing combustible and using SREC). We will have baseline EMA data on smoking events and random time sampling of urges, mood, satisfaction with smoking, as well as context. Then we will have a week of EMA data on the second week of the instructed switch to SREC . We will compare EMA data during baseline to the SREC switch week on the following within subject factors: context of use (alone, with others; location – home; work; in public; presence of other smokers; time of day (e.g., first cigarette of the day); mood prior to use; mood after use; urge prior to use and at random time; satisfaction after use). We will use three-level (observations within weeks within subjects) linear mixed models for continuous outcomes (mood), logistic mixed models for binary outcomes (context), and survival mixed models[59] for time to an event (first cigarette of the day). The main independent variable will be the indicator of EMA week (baseline/switch week) to test whether the outcomes vary by EMA week. We will also control for group (usual flavor/flavor choice) and examine whether the effect of EMA week varies by group. Analyses will also include sex and prior menthol use as covariates.

10.0 Quality Control and Quality Assurance

A detailed and robust quality assurance plan is essential for ensuring the scientific rigor and management of any study. Using our study protocol, good clinical practice, and documented standard

operating procedures, we will have written materials to support all study procedures. We will establish clear study roles and responsibilities that will promote dialogue across staff and ensure proper study execution across roles, with checks built into the overall quality plan at many points. We will provide training materials and procedures and demo versions of key software products or devices (EMA phones) with cases mocked to real-world scenarios to train staff before encountering actual participants. All clinical staff will conduct mock visits with EMA interviews and behavioral counseling under supervisor observation to ensure competence with following study procedures before permitted to operate independently. Dr. Diviak will also observe 10% of each clinical staff treatment sessions in order to ensure the intervention is delivered appropriately. We have several years of senior staff experience with our two-stage screenings process that involves potential participants first completing an online screener, followed by staff phone call completion of a second screener. We have existing REDCap screening and scheduling databases running similar models. For our various data collection instruments, we will have scheduled reviews of collected data as well as random checks. Our quality procedures will involve automated programming/statistical checks executed at the time of individual data collection as well as report listings and aggregate statistics on groups of cases. The Data Manager, Mr. O'Keefe conducts checks weekly or monthly, depending on the data being reviewed. If cleaning edits are appropriate for the quality of the data, all edits will maintain an audit trail of original and final value, reason for edit, date of change, and name of person making the change. Lastly, we will require that coded syntax be used by all data management and analytical staff for any data formatting, editing, and all analysis. All analyses must be reproducible programmatically.

11.0 Data and Safety Monitoring

This trial will be monitored by Robin Mermelstein, Ph.D. (PI), Kathleen Diviak, Ph.D. (Co-I), John O'Keefe (Data Manager), and an independent Data Safety Monitoring Board (DSMB) that will be chaired by a medical safety monitor: Jonathan Klein, MD, MPH, FAAP, Professor of Pediatrics, College of Medicine, UIC. The DSMB will meet at the start of the trial to review the study protocol, safety and ethical issues, and to approve plans for data integrity. Dr. Mermelstein, Dr. Diviak, and Mr. O'Keefe will meet weekly during the data collection phase to review and monitor the following items: participant accrual, participant complaints, participant drop-out, reasons for drop-out, adverse events, and any other problems related to study participation. Data accuracy and completeness will also be monitored weekly. During active recruitment, the DSMB will join these data review meetings quarterly to monitor participant safety.

The data report will be updated on a weekly basis and will include: participant accrual, participant complaints, participant drop-out, reasons for drop-out, adverse events, and any other problems related to study participation. The report will also include preliminary data on cigarette and SREC usage on a participant basis.

An AE is defined as any untoward medical or psychological event experienced by a patient during or as a result of his/her participation in the study that represents a new symptom or an exacerbation of an existing condition whether or not considered study-related based on appropriate medical judgment. SAEs are any adverse experience that results in any of the following outcomes: death, life-threatening event/illness, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, pregnancy resulting in a congenital anomaly/birth defect, or any event requiring medical or surgical intervention to prevent permanent impairment or damage. In this study, this is defined as physician confirmed diagnosis of any of the following: angina pectoris, heart attack, stroke, transient ischemic attack, heart failure, coronary angioplasty or bypass surgery, peripheral vascular disease, and cancer (except for non-melanoma skin cancer). Non-SAEs are all adverse events that do not meet the above criteria for "serious."

AEs will be systematically identified by querying participants at each of the in-person data collection time points after the start of treatment (week 2) through end of treatment (i.e., at weeks 3, 4, 6, 8, 11, and 14) using a standardized AE Patient Query Form to be adapted from Dr. Mermelstein's prior research studies using NRT while reducing cigarettes. AEs discovered outside of those planned evaluations, such as through other administrative interactions between research staff and participants (e.g., appointment reminder or rescheduling calls), will also be documented using the standardized AE form and followed up with to assure participant safety. Research staff will complete the AE forms directly into a centralized REDCap database in these circumstances. Drs. Mermelstein and Diviak will receive an automatic notification from REDCap upon submission of every AE report in order to trigger a review. The study safety monitor (Dr. Klein) will review, adjudicate, and document decisions or request that additional details be gathered from the participant, all

within the secure UIC REDCap web portal. Using this system, real-time AE reports can be generated at any time for the DSMB, UIC IRB, and/or NIDA, for both regularly scheduled reviews as well as in the event of any SAEs requiring expedited reviews.

Expedited reporting. All unexpected SAEs will be reported to the DSMB within 5 business days of discovery, regardless of any judgment of their relatedness to the study treatment. This reporting timeframe is consistent with the UIC IRB's requirements as described below. All relevant information will be reported to the DSMB for each unexpected AE including information about the event and its outcome, dosing history of a suspect medication/treatment, concomitant medications, the participant's medical history and current conditions, and all relevant laboratory data. An initial notification with all related study forms shall be made to the DSMB within 72 hours of the detection of an unexpected SAE. Any additional information about the case that may be obtained after the initial notification shall be communicated to the DSMB in a timely manner. The DSMB may require a conference call to review all the relevant information and the study safety monitor's determination of whether there was any possible relevance to the study and discuss and approve a Corrective and Preventive Action Plan, if warranted.

IRB requirements for AE reporting. The UIC IRB requires that within 5 business days of the PI learning of an unanticipated AE or major protocol deviation, the PI inform the Director of IRB panel and all relevant oversight committees at the university. Within 15 business days of the PI becoming aware of non-SAE, changes in risk/benefit, or events requiring report to the sponsor, these will be reported. This timeline satisfies the NIDA reporting requirements for AEs and unanticipated problems. An annual report will be submitted to the IRB and to the sponsor summarizing all AEs, serious or not.

Reporting Mechanisms of IRB actions to NIDA. The study PI will notify NIDA, through our Program Officer, within 5 days should our IRB put an administrative hold on the project or if the IRB issues a suspension or termination of IRB approval for the study.

Reporting SREC Adverse Experiences to FDA. In our ADVICE/INFORMATION letter from the Center for Tobacco Products at the FDA, they encouraged us to report adverse experiences with the SREC through the CTP Safety Reporting Portal Pathway for Researchers. We plan to follow the same timeline for reporting these events as described above for reporting to IRB and NIDA.

Management of SAEs or Other Study Risks. We believe that the risks of SREC are minimal, given the prevalence of use of e-cigarettes and the consensus that they are far less harmful than conventional cigarettes. SAEs will be immediately reported to the medical monitor, Dr. Klein and to the IRB. Dr. Klein will address these with the participant to ensure that the participant is linked with appropriate follow-up medical care.

We will discuss potential risks with participants at study enrollment and consent. We will discuss with participants that all tobacco use may present some harm, and that no tobacco use is healthy. We will also provide education to participants on the symptoms of nicotine toxicity (nausea and vomiting) so that they are aware and can reduce their exposure if they experience these symptoms. We also will provide participants with education on the recent outbreak of EVALI cases and how to identify if they may be experiencing the early signs and symptoms of an EVALI. At the enrollment visit (during the consent process) and at the end-of-treatment visit, we will tell participants that the long-term safety and health effects of using e-cigarettes is unknown. We will also discuss in-person and include on the information sheet that the SREC device may contain nicotine which can be hazardous to children and pets if ingested, in addition to informing the risk of nicotine use for pregnant and/or nursing women. We plan to discuss the safe and secure storage of the device and pods in their homes. Additionally, we will clearly label the SREC packaging so that participants are aware the SREC is used "for investigational purposes only."

Clinical study staff are the first line of staff to monitor and assess AEs and UPs. These will be assessed at each study visit after week 2. They will be recorded in REDCap responses to short surveys and in written responses to interview questions. Staff will notify Drs. Diviak and Mermelstein about these events during weekly supervision, but Drs. Mermelstein and Diviak will also receive emails as Adverse Event Reports are submitted to the REDCap database. Plans will be developed to manage and monitor AEs and UPs. SAEs will be immediately reported to the medical monitor, Dr. Klein. Dr. Klein will address these with the participant to ensure that the participant is linked with appropriate follow-up medical care. In our REDCap database, we will have a programmed report for AEs and UPs that can be run as needed for review to ensure that our understanding of adverse events and problems is always up to date.

Trial Stopping Rules. This is a low-risk trial and will be conducted over a short time span. Thus, we do not have any formal stopping rules for safety. If at any time during the course of the study, the DSMB judges that the risk to participants significantly outweighs the potential benefits (which is unlikely given the evidence base for the proposed interventions), the DSMB shall have the discretion and responsibility to request all necessary information for detailed analyses, and if warranted, recommend that the study be terminated. Stopping rules for the trial could include stopping because of a significant number of injuries or illnesses that can reasonably be attributed to participation in the study, inability to recruit and measure the required number of participants to conduct the primary outcome analyses, poor intervention quality and delivery, serious deviation from study protocols, or other circumstances that would render the study unlikely to produce scientifically valid findings. The DSMB will carefully weigh the risk of completing the trial as planned against the risk of prematurely stopping the trial for safety or futility.

If participants drop out before the end of the study, we will make every effort to collect their SREC device and all used and unused pods that have been distributed.

Expedited reporting. All unexpected SAEs will be reported to the DSMB within 5 business days of discovery, regardless of any judgment of their relatedness to the study treatment. This reporting timeframe is consistent with the UIC IRB's requirements as described below. All relevant information will be reported to the DSMB for each unexpected SAE including information about the event and its outcome, cigarette and SREC use history, concomitant medications, the participant's medical history and current conditions, and all relevant laboratory data. An initial notification with all related study forms shall be made to the DSMB within 72 hours of the detection of an unexpected SAE. Any additional information about the case that may be obtained after the initial notification shall be communicated to the DSMB in a timely manner. The DSMB may require a conference call to review all the relevant information and the study safety monitor's determination of whether there was any possible relevance to the study and discuss and approve a Corrective and Preventive Action Plan, if warranted.

12.0 Statistical Considerations

Attrition and nonresponse. Despite our efforts, some attrition and missing data are likely. The mixed model does allow missing data and provides valid results under the assumption of missing at random (MAR). MAR means that the missingness can be related to model covariates as well as observed values of the dependent variable and is sometimes termed "ignorable" missingness. As Molenberghs et. al.[60] detail, MAR is a relatively weak and non-restrictive assumption about the missing data. Nonetheless, the possibility of non-ignorable missingness cannot be ruled out and so, as advocated by Molenberghs et. al.[60], we will conduct sensitivity analyses using non-ignorable pattern-mixture and selection models to investigate the robustness of our conclusions across these different models for missing data. These sensitivity analyses apply to the both the longitudinal and EMA models that we have proposed. In particular, in the EMA context we will jointly model the outcomes and EMA prompt missingness, with random subject effects shared by both models. In this way, our model for the outcome will control for a person's propensity to miss EMA prompts.

Power considerations. The proposed sample size of 120 smokers was determined based on the primary aims. In all power calculations, we conservatively assumed an attrition rate of 10%, yielding a sample size of 108 at the end of the study. We will randomize 60 smokers to usual flavor SREC (N=54 at end) and 60 smokers to choice of flavor SREC (N=54 at end). The primary endpoint is the group difference in the rate of combustible cigarettes used at the 12-week timepoint. We will model this outcome across time in a mixed Poisson model. Based on data from our prior study of dual users of cigarettes and e-cigarettes and current experience, the average rate of smoking is expected to be between 11 to 15 cigs/day. With the proposed sample of 54/54 at the 12-week timepoint, we have power of .8 for a two-tailed hypothesis test to detect a relative risk of .75 (reduction to 8.2 cigs/day in the flavor choice group relative to 11 cigs/day in the usual flavor group or reduction to 11.25 cigs/day in choice vs 15 cigs/day in usual flavor). We note that these are conservative estimates of power as these calculations only consider data from the 12-week timepoint, whereas our model will include the longitudinal data from the 12 weeks. In addition, we expect significantly greater reductions in the flavor choice group than we are estimating here given expectations of greater engagement and adherence in the choice group, but these power considerations build in the likelihood that reductions are not sustained. Thus, we believe that these are conservative estimates. In terms of the binary outcome of abstinence at the final 12-week timepoint, we have power = 0.8 for a comparison of abstinence rates of 31.5%

(flavor choice) vs 10.% (usual flavor) for a two-tailed hypothesis test. Again, this is conservative as it is a two-tailed test and only considers data at the 12-week timepoint and attrition of 10%. Thus, we have good power to detect meaningful differences in both smoking rates and smoking/abstinence classification. In addition, given the ample EMA data, we will be able to examine how satisfaction/pleasure from SREC is associated with adherence to SREC and reduction in cigarette rate. For aim 2, which will examine associations between changes in SREC usage and change in health outcomes, again, we conservatively consider power at one timepoint. For this, with the sample size of 108 (allowing for 10% attrition), we can detect a correlation of .262 with power of .8 on a two-tailed hypothesis test. This level of association is between a small and medium effect size[61], and in line with correlations that we have observed in our prior studies.

For aim 3, in terms of the EMA data, given that we are including smokers who smoke 3+cigs/day; we are likely to have many events per day over the week to sample. Even with 3 smoke events/ day; plus 5 random a day – that is likely to give about 30 random events and at least 21 smoke events at baseline across 120 participants, providing ample data for within- and between-subject analyses. As an example, we can consider power for comparing responses from smoking reports to random prompts using simulation. Based on our current data, we assumed an intraclass correlation coefficient between 0.3 to 0.4, and considered power for a binary outcome (e.g., alone vs not alone). We simulated 1000 datasets and estimated a logistic mixed effects model including a random subject effect and fixed effect comparing random prompts and smoking reports. Power is determined as the proportion of datasets in which the null hypothesis of no difference between random prompts and smoking reports is rejected. Under these assumptions, power exceeded 0.8 for an odds ratio of 1.2.

For aim 4, during the switch week we are likely to see the same number of random events (and the SREC events and conventional cigarette events may both occur). Thus, we can examine what are the situations in which they still smoke or contexts in which they can switch. If we assume, conservatively, 20 smoking events and 10 SREC events, with 108 subjects (allowing for 10% attrition) and an ICC between 0.3 and 0.4, we can detect an odds ratio of 1.25 with power = .8 on a two-tailed .05 test. Thus, we have excellent power to detect rather small differences for within-subject comparisons involving cigarette vs SREC reports, even with a modest number of SREC events per person. Power for comparisons to random prompts will be even better.

13.0 Regulatory Requirements

13.1 Informed Consent

Participants will be provided with all the study details, potential risks, and benefits of participation and complete screening for eligibility before scheduling an in-person appointment at our research office to conduct the enrollment/baseline visit. During the enrollment visit, the study staff will review the informed consent document with participants to ensure their understanding of all study procedures, potential risks and benefits, and the voluntary nature of their participation. We review with potential participants the study information that will be shared (and who it is shared with) as well as the information that is not shared with. We let them know that we never use their name or other identifiable information (e.g., birthdate) when sharing the data set, rather their questionnaire and EMA data is shared using a study ID number only. Staff are trained to ask questions to ensure that potential participants understand what is being asked of them and what is involved in participation. The clinical staff receive training on conducting the consent process by Dr. Diviak. The training process stresses the voluntary nature of participating in the research study and providing a clear description of all study activities and requirements so that participants can make an informed decision about if participating in the study is something that they want to do or not. Methods of assessing the understanding of study information will also be covered in the training. Staff will observe Dr. Diviak conducting the consent process, they will practice with non-participants (e.g., other staff) in role-playing situations, and will also be observed and feedback provided before staff conduct a consent process themselves. Staff will need to be cleared to conduct the consent process before working with actual participants.

Signed consent forms will be stored in a locked cabinet in a locked office separate from all other data. Only study staff who require access to the consent documents as part of their study role will have access. We will request a waiver of signed consent for the screening portions of the study, although we will still conduct a consent process for the screening portions. For the online screening survey, potential participants will read a

written statement about the purpose of the screening survey along with the risks and benefits of participating in the screening process. People who are interested in completing the screening survey must indicate that they have read the description and that they agree to complete the screening survey. This agreement is noted in the REDCap screening database.

13.2 Subject Confidentiality

Confidentiality of all data we collect are assured by using a unique numerical identifier for each participant. The master list of name and identifier match is restricted to only personnel who require the match for essential study tasks. The list will reside in a REDCap database kept separate from the other REDCap datafiles that contain questionnaire responses. Materials that contain individuals' names or other important contact information (e.g., mailing address, phone, email) will also be restricted and password protected. Identifying information and data are not stored together. Once collected, an individual's de-identified data will not be released to anyone other than authorized project staff and investigators. The EMA program is password protected and accessing and downloading the data requires a custom download program that can only be accessed by authorized study staff. If a participant were to lose a phone, no one else could access data stored by the EMA program. We have developed extensive procedures and protocols in our current and previous EMA studies with no accidental disclosure or adverse consequences to study participants. We believe that staff training is crucial to ensuring confidentiality. Staff will participate in UIC's human subjects protections training, along with specific, project-focused training and frequent reviews with Dr. Diviak and Mr. O'Keefe (Senior Data Manager) to ensure staff understanding and compliance with project protocols. The code that connects the study ID to name will be destroyed at the end of the funding for this study.

13.3 Unanticipated Problems (UPs)

All staff who work directly with study participants are trained to notify Drs. Mermelstein and Diviak of any UPs resulting from study participation immediately on discovery. UPs may also be reported through participant Adverse Event reporting at each study visit. Drs. Mermelstein and Diviak will receive an automatic notification from REDCap upon submission of every AE report in order to trigger a review. In addition, the Data Safety Monitoring Board will meet and review any UPs. Dr. Mermelstein, Dr. Diviak, and Mr. O'Keefe will meet weekly during the data collection phase to review and monitor the following items: participant accrual, participant complaints, participant drop-out, reasons for drop-out, adverse events, and any unanticipated problems related to study participation. During active recruitment, the DSMB will join these data review meetings quarterly.

All serious unanticipated problems will be reported to the IRB within 24 hours. Serious events are described as untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, creates persistent or significant disability/incapacity, or a congenital anomaly/birth defect. The probability of such occurrences as part of this study is extremely low. Nevertheless, an appropriate Data and Safety Monitoring Plan is in place. If such an event occurs, the PI will immediately notify the entire Data and Safety Monitoring Board and the IRB within 24 hours. The Office of Protection of Research Subjects (OPRS) at the University of Illinois at Chicago has procedures in place to review reports, and the PI is notified if further review, changes to the research protocol or consent form, or other action is required. Dr. Robin Mermelstein will notify NIDA should the UIC IRB review require further action after any serious unanticipated problem is reported.

UIC OPRS also defines unanticipated problems as a breach of confidentiality or subject complaints. OPRS requires that all incidents be reported within ten working days of discovery. For all unanticipated problems, sufficient information shall be obtained from the PI in order to gauge severity and to complete the mandatory OPRS report form. UIC OPRS has procedures in place to review the report form, and the PI is notified if further review, changes to research protocol or consent form, or other action is required.

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