Cigarette Harm Reduction with Scheduled Electronic Cigarette Use

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Cigarette Harm Reduction with Scheduled Electronic Cigarette Use

Neal Benowitz, MD

Dr. Benowitz is Professor of Medicine and Bioengineering & Therapeutic Sciences and Chief of the Division of Clinical Pharmacology Laboratory at Zuckerberg San Francisco General Hospital (ZSFG), a leading site for biomarker assessment of tobacco toxicant exposure. Dr. Benowitz has been conducting research with the university at ZSFG since 1973. His research focus is on the human pharmacology of nicotine in relation to pathogenesis of and individual differences in vulnerability to tobacco-related disease, and the use of pharmacologic data as a basis for public health policies to prevent and reduce such disease. He is the former president of the Society for Research on Nicotine and Tobacco (SRNT), and recipient of the Ove Ferno SRNT Award for Clinical Research on Nicotine and Tobacco. Dr. Benowitz has been a contributing author or editor to six U.S. Surgeon General’s Reports on tobacco, including the 2010 Surgeon General’s Report—How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease. He has served on a number of national and international committees addressing issues in tobacco-related diseases and smoking cessation, including several sponsored by the Institute of Medicine. Authoring over 600 publications, including a state-of-the-art review on nicotine addiction in the New England Journal of Medicine in June 2010, Dr. Benowitz is a leading authority on the human pharmacology of nicotine and nicotine addiction.

Gideon St. Helen, PhD

Dr. St. Helen is a toxicologist whose research focuses on utilizing biomarkers to characterize human systemic exposure to tobacco toxicants for the purpose of informing tobacco product regulation, epidemiologic research, risk assessment, and understanding of tobacco-related health disparities. He completed his postdoctoral fellowship in the Benowitz laboratory through the UCSF Center for Tobacco Control Research and Education (CTCRE), honing skills in clinical research, including studies on nicotine pharmacology and nicotine addiction. He has first and co-authored several studies on nicotine and carcinogen intake among cigarette smokers, users of alternative tobacco products, and nonsmokers. He has recently completed studies on the clinical pharmacology of a variety of electronic cigarettes and the effects of e-cigarette liquid flavors on nicotine delivery, retention, pharmacokinetics, and subjective effects. Dr. St. Helen is a PI on a grant to examine the site of e-cigarette aerosol deposition in human airways using PET imaging (TRDRP-251R-0028), and co-investigator of studies on the clinical pharmacology of e-cigarettes in dual tobacco/e-cigarette users (R01DA039264, PI Benowitz) and THC oils when vaporized in e-cigarettes (3R01DA039264-02S1). Dr. St. Helen’s roles on the proposed project include contribution to study design and start-up, assist in procedures on the research ward, pharmacokinetic analysis, data analysis, and preparation of manuscripts for publication.

Peyton Jacob, PhD

Dr. Jacob has carried out research on the chemistry, pharmacology, and toxicology of tobacco and other drugs of abuse for over 30 years. Dr. Jacob is the Director of the Clinical Pharmacology Research Laboratory at UCSF-ZSFG and the Laboratory Director of the Tobacco Biomarkers Core for the UCSF Helen Diller Family Comprehensive Cancer Center, a core facility for the UCSF FAMRI Bland Lane Center of Excellence on Secondhand Smoke, the California Consortium on Thirdhand Smoke, and the UCSF Tobacco Center of Regulatory Science (TCORS). He has a demonstrated record of successful and productive research on the metabolism and disposition of psychoactive drugs, and development of biomarkers of exposure to carcinogens and other toxic substances. He has expertise in the development of methods for quantitative analysis organic small molecules, in particular tobacco alkaloids and other psychoactive substances, therapeutic drugs, and toxic substances. He has developed methods for the synthesis of analytical standards and stable isotope-labeled internal
standards for mass spectrometric methods, and labeled compounds for human metabolic studies. Dr. Jacob’s role in this project includes supervising the analytical chemistry laboratory, assisting in biomarker data analysis and data interpretation, and working with Dr. Benowitz and other Co-Investigators in writing reports and manuscripts for publication.

**Delia Dempsey, MD**

Dr. Dempsey has been associated with the research group headed by Dr. Neal Benowitz since 1991. She retired in June 2012 and returned (recalled) to continue with the same research group. She is also a volunteer physician at the ZSFG Pediatric Asthma Clinic. Dr. Dempsey’s research has predominantly been in the area of nicotine metabolism, smoking, and secondhand & third hand smoke exposure, with a special emphasis on infants and children. Dr. Dempsey was a contributing Author, to Chapter 8. Reproductive and Developmental Effects in the 2010 Surgeon General’s Report, How Tobacco Smoke Causes Disease.

**Kevin Delucchi, PhD**

Dr. Delucchi is a Professor of Biostatistics in the UCSF Department of Psychiatry and in the UCSF Division of Epidemiology and Biostatistics. He directs the Informatics and Statistical Core of the FDA/NIH funded Treatment Center of Regulatory Science and for 20 years was Director of the Quantitative Core of the NIDA-funded San Francisco Treatment Research Center. He is a faculty member and co-director of a NIDA-funded T32 training grant and faculty on the R25 Mentoring Early-Career Scientists for Drug Abuse Research Careers. Dr. Delucchi is an active collaborator, consultant, and co-author with numerous investigators, post-doctoral Fellows and other trainees at UCSF. He has a long history of tobacco related research such as proposed here and has collaborated with Dr. Benowitz previously. He will serve as a Co-Investigator and help direct data processing, analyses and interpretation of results.
STUDY SITES

Primary Location

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BACKGROUND & PROJECT SUMMARY

Harm Reduction with Use of E-Cigarettes

One of the major reasons cited for the use of electronic cigarettes (EC) is to reduce harm from smoking. This might be accomplished by smoking fewer tobacco cigarettes (TC) per day, or switching completely from TC to EC. Based on studies published to date when smokers switch from TC to EC their exposure to TC toxicants, including carbon monoxide (CO), tobacco specific nitrosamines (TSNA), polycyclic aromatic hydrocarbons (PAH), and volatile organic compounds (VOCs) are reduced to levels close to or same those of non-smokers. A few studies report that switching can result in clinical harm reduction, with improved symptoms or functional tests in smokers with asthma, chronic obstructive lung disease (COPD), and hypertension. On the other hand there have been reports of increased bronchitis symptoms in youth who use EC, and biological plausibility that EC could aggravate cardiovascular disease (CVD).

The potential benefit of reducing daily TC use supported by EC use is less clear. Epidemiologic data in smokers indicate that there is a linear relationship between cigarettes per day and risk of cancer and COPD, suggesting that reduced TC use should reduce risk. However for CVD, the relationship is non-linear, with a sharp increase in risk with only a few CPD, and a much shallower CPD vs risk curve at higher levels of smoking, suggesting that reduced TC would have little effect on CVD risk. Much of our prior research and the emphasis of the present proposal is on CVD risk. Our proposal seeks to compare toxicant exposure and biomarkers of cardiovascular (CV) effects (hemodynamic, thrombogenic, inflammatory, and oxidative stress biomarkers) with dual EC/TC use compared to use of EC and TC alone. Data on the effects of dual use will address a major gap in EC harm reduction research.

Rationale for Scheduled EC Use as a Model for Dual TC/EC Use

A key component of our study design employs scheduled EC use as a platform for studying dual TC/EC use. Our rationale is several-fold. First, there is a precedent for prescribed a minimum number of doses of nicotine medications (e.g. gum or inhalers) to smokers to support reducing TC consumption in preparation for quitting. In contrast, when smokers are instructed to use gums as desired, they tend not to use very many gums, and do not get enough nicotine to support cigarette reduction. Our subjects will be primary TC smokers who have also used EC. We believe that fixed dosing of the Standardized Research E-Cigarette (SREC) will ensure adequate nicotine intake from EC to support smoking fewer TC per day. Second, one of our main objectives is to examine harm reduction with dual TC/EC use. From past experience, when given the choice of ad libitum use of either TC or EC, most smokers will choose TC. We propose to have subjects use SREC 8 times per day,
while allowing ad libitum use of TC, to generate our dual use condition for studying health related effects compared to TC alone. Eight sessions of SREC use will give adequate time (90 min) between SREC sessions to smoke a reasonable number of TC. Third, this paradigm allows us to examine the question of titration of nicotine intake - that is, will smokers during dual SREC/TC take in similar amounts of nicotine during the day compared to TC only use?

### Nicotine Delivery and Titration

Tobacco and EC are designed to be nicotine delivery devices. While the typical cigarette delivers 1–1.5 mg nicotine systemically to the smoker, there is wide individual variability. The average nicotine delivery from the SREC looks to be similar to that of a cigarette (NIDA webinar), but data on individual variability is not yet available. One objective of our study is to examine pharmacokinetics of nicotine with a standardized puffing protocol (similar to that we and others have used in published studies), comparing TC and SREC. While the puffing interval is prescribed (every 30 seconds) and number of puffs prescribed (10), there is still considerable individual variation due to duration and intensity of puffing and inhalation pattern. We will compare nicotine exposure and estimate systemic dose for SREC and TC, and will determine whether individuals titrate doses even with a standardized use protocol. We have also found in a prior study that in some subjects the peak nicotine level is lower and occurs later with EC vs TC, and we will assess whether such differences are seen with the SREC. Nicotine dosing and absorption kinetics are important determinants of reward and abuse liability for different products. We will compare reward and relief of withdrawal symptoms while using SREC and TC. In TC smokers an important piece of evidence supporting the idea of nicotine addiction is that they take in a relatively constant dose of nicotine from day to day. This is seen when the nicotine delivery product changes, such as switching from high- to low-nicotine yield TC. Thus, TC smokers adjust their smoking behavior to maintain their desired levels of nicotine intake: they “titrate” their use and nicotine dosage. While nicotine titration might not be entirely possible when using a product in a standardized puffing protocol, it would be more likely to be observed with ad libitum use. Our proposed study addresses the question of whether nicotine reinforces use of SREC in the same way it does for TC. Our circadian measurement of blood nicotine levels allows us to assess daily intake of nicotine and to examine titration across three conditions: TC alone, SREC alone and dual SREC/TC use. In addition, we will explore whether potential changes in nicotine intake when switching products are associated with nicotine withdrawal symptoms or craving. Titration of nicotine intake may be an important question for predicting EC use patterns in harm reduction.

The pattern of EC puffing appears to differ from that of TC use. One key factor is that smokers must smoke TC in concentrated time intervals because the cigarettes will burn down after lighting regardless of the number of puffs taken, whereas ECs are activated and
deliver nicotine only when the user chooses to do so. TC users typically take 8-10 puffs of a cigarette over 8 minutes or so, and the pattern of use throughout the day is variable, with some smoking more consistently throughout the day, while others cluster smoking in the morning or in the evening. In contrast, because EC do not burn down when not in use, users tend to use the products more regularly throughout the day rather than clustering use, which suggests that the rewarding effects are different for EC vs TC use. There appears to be less “peak seeking” and more “trough maintaining” behavior from EC compared to TC. “Peak seeking” refers to the pattern of clustered smoking that result in intermittent spikes of high concentrations of nicotine delivery to the brain and is believed to be linked to smoking for pleasure and stimulation. “Trough maintaining” refers to the pattern of regular smoking throughout the day that sustains nicotine blood levels and is believed to be linked to smoking to avoid withdrawal symptoms. There have been few systematic studies of temporal patterns of EC use, and no comparisons within subjects of patterns for EC vs TC use. One of the objectives of our study is to examine and compare daily patterns of ad libitum use or SREC vs TC in a circadian study. Subjective data on reward and withdrawal symptoms will provide insight into the reasons for these patterns of self-administration.

Safety of SREC

EC are believed to be less hazardous than TC because there is no combustion of tobacco to produce the various toxic combustion products (oxidants, combustion-derived carcinogens, and toxic gases) which are thought to be responsible for most of the harmful effects of smoking. ECs do deliver nicotine, propylene glycol (PG), vegetable glycerin (VG), flavorants, and - particularly at higher temperatures - thermal degradation products such as formaldehyde, acetaldehyde, and acrolein. Some devices generate benzene, a human carcinogen. Others deliver low levels of minor tobacco alkaloids and tobacco specific nitrosamines, depending on the extent of purification of nicotine.

Nicotine has been shown to have some potentially adverse effects on heart rate, vascular function, insulin sensitivity, and the fetus of mothers who smoke. However, nicotine is primarily “harmful” because it mediates addictive use of TC. The potential adverse CV effects of nicotine have long been of concern. As discussed in two recent reviews from this laboratory, the main CV effect of nicotine is sympathetic nervous system stimulation, most clearly manifested as increased heart rate and catecholamine release (particularly epinephrine). Sympathetic nervous stimulation may contribute to CV events in people with pre-existing CVD, including sudden death due to arrhythmia. We have done extensive research on the CV effects of nicotine in the past and have found a dose-response such that low levels of nicotine produce near maximal CV responses. Single use of EC products has been shown to increase heart rate and blood pressure, as expected. In a previous EC study, we have studied for the first time the circadian CV effects of daily ad libitum use of EC. We found that HR was increased throughout the day with TC use compared to no nicotine, with
an intermediate effect of EC. We also demonstrated similar response for urinary excretion of epinephrine. We propose to conduct a similar analysis for SREC vs TC, and for the first time examine the effects of dual use on the CV parameters. We hypothesize that dual use will have persistent CV effects throughout the day, with similar effects on heart rate, blood pressure and catecholamine release as for TC. One of the objectives of our proposal is to examine the circadian CV effects of nicotine from SREC alone compared to TC alone compared to dual use.

There is concern about potential health effects of chronic inhalation of the vaporized base components (PG and VG) of the e-liquid. Goniewicz et al tested vapors generated from 12 early generation brands of EC and found widely varying levels of toxic substances, including acrolein, formaldehyde, acetaldehyde, toluene and TSNAs. Depending on the product and toxicant, the levels of the toxicants were 9–450 times lower than in TC smoke and in some cases comparable to trace amounts found in a reference nicotine inhaler. However, recent studies have found that at the high battery voltages used to generate high EC temperatures in more advanced devices, formaldehyde, acetaldehyde, and acrolein levels can be as high as those generated by TC. Acrolein, which is believed to be a major contributor to smoking-induced cardiopulmonary disease, is metabolized to 3-hydroxypropylmercapturic acid. PG can form propylene oxide (an IARC class 2B carcinogen) on heating, which is metabolized to 2-hydroxypropylmercapturic acid. Benzene, which has been reported to be a thermal degradation product of e-liquids containing PG, VG and benzoic acid, is metabolized to phenylmercapturic acid.

Urine levels of mercapturic acid biomarkers of acrolein, propylene oxide, benzene, and other potentially toxic volatile organic compounds (VOCs) are routinely measured in our laboratory using a method that we developed. One of the objectives of our study is to measure urinary biomarkers of exposure to VOCs in the same subject with SREC-only vs TC-only use compared to dual use. We chose to focus on acrolein, propylene oxide, and benzene because their mercapturic acid metabolites have relatively short half-lives enabling us to assess exposure due to EC vs TC after only two or three days of use. This is in contrast to NNAL, which has a half-life of 10-16 days resulting in carryover from TC to EC conditions. We will still measure NNAL because there will be a substantial decline in levels if NNAL is present at lower levels in EC, but this will be a secondary measure. Unfortunately, since formaldehyde and acetaldehyde are endogenous substances that are rapidly metabolized we have no way to assess exposure to these EC aerosol constituents.

Polycyclic aromatic hydrocarbons (PAHs) are a class of compounds that are associated with an increased risk of lung and other cancers. We have done extensive research on PAH urine biomarkers, using a method we developed. We expect to see a marked decline in PAHs comparing TC and SREC, as we have reported in another recent EC study. As is the case for VOC metabolites, PAH metabolites have a short half-life so that we can see new
steady state levels within two or three days. Since PAH emissions from ECs are quite low, the main use of PAH measures will be to examine the difference between TC alone and dual SREC/TC use, as related to the harm reduction question.

Heating of e-liquid generates oxidizing chemicals, including reactive oxygen species. Levels of oxidants in EC aerosol are reported to be orders of magnitude lower than those in cigarette smoke, but higher than that of air pollution. However oxidant generation has been reported for only a few products and use conditions. We will assess a biomarker of lipid peroxidation, reflecting oxidative stress. Some EC aerosols have also been shown to contain metals (tin, silver, iron, nickel, aluminum, and chromium) thought to be derived from the degradation of the heating elements, and which might contribute to cardiac toxicity, but resource limitations prevent measurement of metals in samples from our subjects.

Cigarette smoking causes CVD due to actions of tobacco smoke that produce oxidative stress, endothelial/dys function, platelet activation and thrombosis, and inflammation. Of note, while our focus is CVD risk, many of these same mechanisms also contribute to cancer and pulmonary disease caused by cigarette smoking. While it is not feasible to study actual CV events from EC in a two year study of healthy volunteers, we propose to study biomarkers of CV effect that are believed to predict risk, and to compare effects of TC, SREC, and dual use. We have selected biomarkers that have shown to be different TC smokers vs non-tobacco users and which are expected change within a few days during specified product use.

**Biomarkers to Distinguish EC from TC Use**

It is important to have biomarkers to distinguish EC from TC use for purposes of validating smoking abstinence in EC treatment trials and for epidemiology studies assessing the health effects of EC vs TC. NNAL might be a useful marker for long term abstinence from tobacco, but with a half-life of 10-16 days it can take 2-3 months to be fully eliminated from the body. We propose the use of anabasine, anatabine, and nicotelline to assess tobacco use in users of EC. We have used anabasine/anatabine in the past to discriminate TC from NRT use. However, many EC products contain substantial levels of anabasine and anatabine, some in a similar proportion relative to nicotine as is found in TC smoke, so that for these liquids, anabasine/anatabine cannot be used to discriminate. Anabasine and anatabine levels in the SREC are reported to be quite low (NJOY), such that we can test these as potential markers. We think nicotelline is particularly useful as a marker of TC exposure as we have shown that nicotelline is mostly generated from anatelline (another minor tobacco alkaloid) in the combustion of tobacco and is an excellent marker of the particulate phase of TC, with a shorter half-life than NNAL allowing for assessment of recent TC use. Our preliminary data indicate that very little if any nicotelline is generated from EC use, but
large amounts are generated from TC use. We have developed novel urine assays for exposure to minor tobacco alkaloids, including anabasine, anatabine, and nicotelline. A study objective of our proposal is to evaluate minor alkaloids, particularly nicotelline (the ratio of nicotelline to cotinine or to total nicotine equivalents in urine) as a biomarker to distinguish EC vs TC use. In addition, by determining the ratio of minor alkaloids urine to plasma nicotine (area under the plasma concentration time curve over 24 hr) with SREC and TC alone, we can test whether the minor alkaloids can be used to predict the extent of TC use and exposure to tobacco toxicants derived from TC during dual use.

**Preliminary Work**

The Benowitz Research Group has studied the role of nicotine in the control of TC smoking behavior for more than thirty years. This has included studies of the pharmacokinetics of nicotine with various products, studies of titration with switching from high to low yield cigarettes, CV effect studies and numerous studies of biomarkers of tobacco toxicant exposure. Dr. Benowitz has published several recent papers on EC, including reviews of the CV safety of nicotine and ECs, and discussions of regulatory issues related to nicotine.

Dr. St. Helen has published experimental studies on the clinical pharmacology of EC, including studies of nicotine pharmacokinetics and retention, EC use patterns, CV and subjective effects of EC, and influence of flavors on the clinical pharmacology of EC. Dr. Jacob has developed many novel analytical chemistry methods to measure biomarkers of tobacco exposure that have been used in our research and research of others for many years.

The Benowitz research team is currently conducting an NIH-funded study of dual TC/EC users who are studied as inpatients while using TC alone, EC alone, or no tobacco product. A number of different EC devices are being studied, and we are assessing EC exposures as a function of type of device. Examples of data collected from this study are shown in Figures 1 – 3. Thus we are experienced with the study design that is proposed and well positioned to expeditiously conduct the proposed study of harm reduction with SREC.
1 INTRODUCTION AND STUDY DESIGN

1.1 RESEARCH QUESTION
What are differences in the addictiveness and safety of electronic cigarette (EC) and tobacco (TC) use?

1.2 STUDY OBJECTIVES

1.2.1 Study Objective #1
To characterize nicotine delivery, systemic exposure and effects from SREC:
In daily cigarette smokers with a history of EC, instructed to use only SREC or TC for a week at a time, we will address the following questions:

1. In a standardized use session, how does nicotine delivery, peak nicotine concentration and time of peak nicotine concentration compare for SREC vs TC use?
2. What is the systemic exposure to nicotine from daily use of SREC, and how does the daily intake of nicotine during ad libitum use compare for SREC vs TC, and is there absolute or relative titration of nicotine intake when switching from one to the other?
3. How do satisfaction, reward, craving and withdrawal symptoms, and perception of risk compare with daily SREC vs TC use?
4. How does the pattern of puffing compare for SREC vs TC use? Are there similar patterns of regular vs clustered use within subjects?

1.2.2 Study Objective #2
To assess aspects of harm of SREC use compared to TC alone use

5. What are the levels of exposure of tobacco smoke toxicants [particularly volatile organic compounds (VOCs) and polycyclic aromatic hydrocarbons (PAHs)] for SREC-alone vs TC-alone use?

6. How do the cardiovascular effects (circadian heart rate, blood pressure, urinary catecholamine excretion), and effects on biomarkers of platelet activation/thrombosis, oxidant stress and inflammation compare for use of SREC-alone vs TC-alone?

1.2.3 Study Objective #3
To assess nicotine exposure and aspects of harm with dual SREC/TC use compared to TC alone use
7. What is the impact of scheduled SREC use (8 times per day) on ad
libitum TC use, including patterns of use, systemic exposure to nicotine
and subjective effects?
8. What is the impact of dual use of SREC and TC on levels of tobacco
smoke toxicants, cardiovascular effects and biomarkers of inflammation
and oxidant stress compared to TC alone?
9. With dual use of SREC and TC, is there absolute or relative titration of
daily nicotine intake compared to TC use alone?

1.2.4 Study Objective #4
To validate biomarkers to distinguish EC from TC use

10. What is the sensitivity and specificity of the ratio of anabasine or nicotelline to
nicotine metabolites (cotinine or total nicotine equivalents) in urine when used
to distinguish SREC vs TC use? Can these ratios be used to determine changes
in nicotine and toxicant exposure from TC alone compared to dual SREC and TC
use?

1.3 STUDY HYPOTHESIS
We hypothesize that dual use will have persistent CV effects throughout the day,
with similar effects on heart rate, blood pressure, and catecholamine release as for
TC use.
2 STUDY DESIGN

2.1 DESIGN SUMMARY
This is an observational, crossover study that will examine use behaviors, chemical exposures, and biological effects of SREC compared to TC use in subjects confined to a research ward setting.

2.2 ENROLLMENT TARGET
We will enroll 20 participants. We estimate that we can facilitate 1-2 participants per month due to the length of the study (approximately 23 days per subject). The intensity of the assessments will make it difficult to study more than 2 participants at a time.

2.3 STUDY TIMELINE
• Preparation for this study began 04/01/2017
• Application submitted to the IRB: 08/11/2017
• Approval date: 09/05/2017
• Expiration date: 09/04/2018
• Estimated start date: 03/01/2018
• Estimated end date: 02/29/2020

2.4 ELIGIBILITY
Potential participants will express interest in participation by filling out the secure REDCap survey hyperlink from advertisements, the UCSF Tobacco Research websites (e.g., Facebook), or by emailing the UCSF Tobacco Research Center email address. Participants will be contacted to take part in a confidential email screening to determine if they are eligible to come in for an in-person screening visit. At the in-person screening visit, participants will fill out case report forms (TC & EC use, medical history, etc.), the Clinical Research Coordinator (CRC) will take physiological measurements (blood pressure, height, weight, expired CO, etc.), and the participants will provide sample collections (urine and saliva). The participant’s study chart will be reviewed by the Study Physician in order to determine study eligibility.

All individuals interested in participating and who meet the inclusion/exclusion criteria will be invited to be part of the study. Inclusion criteria are described below.

2.4.1 Inclusion Criteria
• Healthy on the basis of medical history and limited physical examination.
  o Heart rate < 105 BPM*
- Systolic Blood Pressure < 160 and > 90*
  - Diastolic Blood Pressure < 100 and > 50*

*considered out of range if both machine and manual readings are above/below these thresholds

- Body Mass Index ≤ 38.0
- Current regular “dual” user of both EC and TC
  - EC device use at least once in the past 30 days
  - Daily conventional TC use (≥ 5 CPD for past 30 days)
  - Saliva cotinine ≥ 50 ng/ml and/or NicAlert = 6
- Age: ≥ 21 years old

2.4.2 Exclusion Criteria
- Medical
  - The following unstable medical conditions:
    - Heart disease
    - Uncontrolled hypertension
    - Thyroid disease
    - Diabetes
    - Hepatitis B or C or Liver disease
    - Glaucoma
    - Prostatic hypertrophy
- Psychiatric
  - Current or past schizophrenia, and/or current or past bipolar disorder
  - Adult onset ADHD (if being treated)
  - Participants with current or past depression and/or anxiety disorders will be reviewed by the Study Physician and considered for inclusion
  - Psychiatric hospitalizations are not exclusionary, but study participation will be determined as per Study Physician’s approval
- Drug/Alcohol Dependence
  - Alcohol or illicit drug dependence within the past 12 months with the exception of those who have recently completed an alcohol/drug treatment program
  - Positive toxicology test at the screening visit (THC okay)
  - Methadone replace therapy
- Psychiatric Medications
  - Current regular use of any psychiatric medications with the exception of SSRIs and SNRIs and current evaluation by the Study Physician that the participant is otherwise healthy, stable, and able to participate.
- Medications
o Use of medications that are inducers of nicotine metabolizing enzyme CYP2A6 (Example: rifampicin, dexamethasone, phenobarbital, and other anticonvulsant drugs).

o Use of medications for cardiovascular conditions including hypertension (Example: beta and alpha-blockers).

- **Other/Misc. Health Conditions**
  - Oral thrush
  - Fainting
  - Untreated thyroid disease
  - Other “life threatening illnesses” as per Study Physician’s discretion

- **Pregnancy**
  - Pregnancy (self-reported and urine pregnancy test)
  - Breastfeeding (determined by self-report)

- **Use of Other Tobacco Products (OTP)**
  - Any of the following products in combination more than 15 times in the past month
    - smokeless tobacco
    - pipes
    - cigars, cigarillos
    - blunts, spliffs
  - Concurrent use of nicotine-containing medications (Example: nicotine patch, lozenge, gum).

- Concurrent participation in another clinical trial.

- Inability to communicate in English.

### 2.4.3 Eligibility Determination

After completion of in-person screening procedures, the CRC will complete an Eligibility Checklist which lists all inclusion/exclusion criteria and the participant’s status based on responses in the case report forms. The Project Manager and CRC will review the Eligibility Checklist after the saliva cotinine results are available.

The Project Manager and CRC will refer to the Study Physician or Principal Investigator if the participant:

- Currently takes any medications on schedule or as needed
- Has current or past depression and/or anxiety disorders
- Has any psychiatric hospitalizations in medical history

The Study Physician will review the information and sign off on the Eligibility Checklist or indicate that the participant is ineligible. If none of the above
conditions are present, the CRC and Project Manager will sign off on Eligibility Checklist without Study Physician review.

The participant will be notified of eligibility via phone or email after this review.

2.4.4 Reassessment of Eligibility
Eligibility may need to be reassessed if the following conditions occur: the orientation visit is out of window (e.g. 90 days past from screening visit), and/or 30 days have passed since the time of the screening visit.

2.4.4.a Outside Orientation Visit Window
If the participant is outside of their orientation visit window of 90 days, the screening visit will be repeated. The original screening visit data will remain in the study chart, however it will not be used for analysis. The participant will repeat all visit procedures, forms, and provide a saliva sample to be re-sent for analysis.

2.4.4.b 30 Days Past Screening Visit
If 30 days have passed since the screening visit, in order to ensure that no significant changes have occurred in a participant’s current medical status and smoking/vaping habits, the CRC will review some eligibility items. This will occur if the participant is more than 30 days, but less than 90 days outside of their screening visit window. The CRC will ask the following over the phone:

- if there are any new medications
- if they have seen a physician for any medical/psychological reason
- if they are still using their e-cigarettes and tobacco cigarettes as indicated at the in-person screening visit

If any significant changes have occurred, the CRC and Project Manager will meet to discuss and complete another Eligibility Checklist based on current participant responses.

2.5 IDs & Assignment

2.5.1 Study IDs
At the start of the phone screen, participants will automatically be assigned a REDCap ID which will start at the number “1” and be in sequence of the order of participants screened. The email screen database will also be numbered sequentially by participant, starting at 1000. These two REDCap databases will later be merged to become one database containing all entries for those screened by
phone and by email for this study. Participants will be assigned a REDCap ID regardless of their eligibility status.

Participants who are eligible for an in-person screening visit will be assigned a unique Study ID upon consent to participate in the study. This Study ID will begin with the “#####” to refer to the CTSI-5B study number, which is how the study is referred to at the research ward. These numbers (to be determined after in-service meeting with CTSI-5B) will be followed sequentially starting from 001. For example, the first participant enrolled will have a Study ID of #####-001.

The Screening Visit Log will keep track the REDCap IDs, and Study IDs (if consented). This log will be maintained as a hard and electronic copy.

2.5.2 Assignment Procedure
The participant will be assigned to one of two groups:

1) Standardized Research Electronic Cigarette (SREC) only for Study Block #1 and Tobacco Cigarette (TC) only for Study Block #2.

   OR

2) Tobacco Cigarette (TC) only for Study Block #1 and Electronic Cigarette (EC) only for Study Block #2.

The participant will not be considered for assignment until it has been verified that he/she is eligible and the Eligibility Checklist has been signed. The participant will be tentatively assigned to one of the two groups when he/she is scheduled for an orientation visit.

The CRC will purchase the tobacco products. The final product assignment will take place at the orientation visit when the participant is physically present at the CTSI-5B research ward. The CRC will refer to the “Assignment Tracking Log,” input the participant’s initials, product assignment, and date he/she is assigned to that condition. Assignment does not necessarily reflect the sequence of the participant’s consent in the study, but rather when he/she is booked for the start of orientation. That time course will vary based upon participant, CRC and CTSI availability.

If a participant drops out or is lost to follow-up (LTFU) during the study, he/she will not be replaced. The assignment schedule will continue as assigned, and the PI can decide to enroll additional participants to compensate for non-completers.
2.6 PARTICIPANT WITHDRAWAL

2.6.1 Dropout Definition
If a participant declares he/she is no longer interested in completing the study, he/she will be considered a “dropout.” Once given “dropout” status, the participant can no longer contribute to the study.

2.6.2 Dropout Compensation
If participant decides to stop participating in the study prior to starting the inpatient portion of the study, he/she will only receive compensation for the Screening Visit ($30) and no compensation will be given for the inpatient portion.

If a participant decides to drop out during the inpatient study, compensation will be pro-rated for completed visits.

2.6.3 Lost to Follow-Up
If a participant is unable to be contacted and does not respond to calls from the Clinical Research Coordinator, he/she will be considered “lost to follow-up” (LTFU).

If a participant is considered LTFU, every effort will be made to contact him/her.

2.6.3.a Contact Attempts
After three unsuccessful phone and email contact attempts, a letter of intent to contact will be mailed to the participant’s home address. This letter will inform the participant that they will be formally withdrawn from the study by the date that is 90 days past the last point of contact. It will also include details on the remaining study compensation available if procedures were continued. If the participant fails to contact the CRC after this outreach, and 90 days have passed since last communication, he/she will be considered “lost to follow-up”. No further outreach will be conducted. Once given “LTFU” status, the participant can no longer contribute to the study.

2.6.3.b Returning to Visit Procedures
If a formerly lost participant returns, before starting the inpatient portion of the study, the reassessment of eligibility steps outlined in Section 2.3.4 of this manual will be followed. If the participant is LTFU during some point in his/her inpatient portion, there will not be the option to repeat this.
3 STUDY SCHEDULING

3.1 VISIT SCHEDULE
The Study Visit chart below describes the schedule of visits and procedures.

### Study Block Week #1: SREC-only or cigarette only (computer randomized)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs</td>
<td>Fri</td>
<td>Sat</td>
<td>Sun</td>
<td>MONDAY</td>
<td>TUESDAY</td>
<td>WEDNESDAY</td>
</tr>
<tr>
<td>&lt; -------- At Home ----------- &gt;</td>
<td>&lt; --------------------------------- Hospital --------------------------------- &gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SREC/Usual product use as regular</td>
<td>Standardized Session</td>
<td>Free use</td>
<td>Free use</td>
<td>Circadian blood draws</td>
<td>Free use</td>
<td>24-hr urine collection</td>
</tr>
<tr>
<td>Daily Diary</td>
<td>4-hr abstinence and blood draws</td>
<td>24-hr BP/HR monitoring</td>
<td>24-hr urine collection</td>
<td>24-hr urine collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Followed by Free use</td>
<td>1 blood draw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Study Block Week #2: Alternate Product from Week #1

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs</td>
<td>Fri</td>
<td>Sat</td>
<td>Sun</td>
<td>MONDAY</td>
<td>TUESDAY</td>
<td>WEDNESDAY</td>
</tr>
<tr>
<td>&lt; -------- At Home ----------- &gt;</td>
<td>&lt; --------------------------------- Hospital --------------------------------- &gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged from the hospital Thursday morning</td>
<td>Standardized Session</td>
<td>Free use</td>
<td>Free use</td>
<td>Circadian blood draws</td>
<td>Free use</td>
<td>24-hr urine collection</td>
</tr>
<tr>
<td>SREC/Usual product use as regular</td>
<td>4-hr abstinence and blood draws</td>
<td>24-hr BP/HR monitoring</td>
<td>24-hr urine collection</td>
<td>24-hr urine collection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Diary</td>
<td>Followed by Free use</td>
<td>1 blood draw</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Study Block Week #3: Standardized SREC Use & Free Use of both products

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thurs</td>
<td>Fri</td>
<td>Sat</td>
<td>Sun</td>
<td>MONDAY</td>
<td>TUESDAY</td>
<td>WEDNESDAY</td>
</tr>
<tr>
<td>&lt; ------------ At Home ------------&gt;</td>
<td>&lt; ---------------------------------- Hospital ----------------------------------&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Discharged from the hospital Thursday morning
- Normal/Usual product use as regular
- Daily Diary

<table>
<thead>
<tr>
<th>Assessment Point</th>
<th>Maximum Time allowed from Phone/Email Screen</th>
<th>Maximum Time allowed from Screening Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone/Email Screen</td>
<td>30 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Screening Visit</td>
<td>120 days</td>
<td></td>
</tr>
<tr>
<td>Orientation</td>
<td>120 days</td>
<td>90 days</td>
</tr>
</tbody>
</table>

### 3.2 SCHEDULE OF ASSESSMENTS

#### 3.2.1 Visit Windows

Table 1 describes the schedule of visits in relation to the start point of the Phone/Email Screen. Ideally, participant assessments will fall within the designated windows.

<table>
<thead>
<tr>
<th>Assessment Point</th>
<th>Maximum Time allowed from Phone/Email Screen</th>
<th>Maximum Time allowed from Screening Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone/Email Screen</td>
<td>30 days</td>
<td>90 days</td>
</tr>
<tr>
<td>Screening Visit</td>
<td>120 days</td>
<td></td>
</tr>
<tr>
<td>Orientation</td>
<td>120 days</td>
<td>90 days</td>
</tr>
</tbody>
</table>

Every effort should be made to enroll and run eligible participants. Thus, if participants are outside of their screening visit or orientation visit windows, reassessment of eligibility will occur as described in Section 2.3.4.

#### 3.2.2 Study Days

Due to CTSI closure on weekends, participants must come in for their Orientation Visit on a Thursday morning. Orientation Visits conducted on Thursday mornings allow for the first and second inpatient admissions to take place on Monday mornings without the issue of weekend closures, and allow for study completion on Fridays.
4 RECRUITMENT METHODS

Our methods of recruitment will be as follows:

- Postings to craigslist and Facebook (paid and free sections)
- Flyers posted in mostly institutional settings (colleges, career centers, churches) and left at vape and smoke shops
- Newspaper ads (typically Bay Guardian, SF Weekly, East Bay Express)
- Blogs, google+ and social networking sites (e.g., Facebook, Reddit, etc)
- Contact of prior callers or study participants who have given permission for re-contact as documented either in the consent form for the prior study or in our phone screening database.

Individuals who respond to recruitment postings/flyers will be screened initially by REDCap survey to determine potential eligibility. Based on this initial assessment they may be asked to come to the UCSF Tobacco Research Center for an in-person screening visit. Additionally, participants from previous studies at the UCSF Tobacco Research Center, who appear to be eligible for the study will be re-contacted and asked if they are interested in participating.

4.1 PRELIMINARY REDCAP SCREENING

Individuals who see the ad will be prompted to click on a hyperlink which will lead them to a preliminary screen on REDCap, or email the UCSF Tobacco Coordinator email address for more information.

The preliminary REDCap screen is a short survey in which the participants provide the following information:

- Contact information
- E-Cigarette/Tobacco Cigarette product use
- Prescription Medication Use
- Exclusionary medical conditions

This REDCap survey is programmed to generate a report of eligible participants. For example, a parameter is set for cigarettes per day to only include participants who smoke ≥5 cpd in the report. The information for eligible participants will be exported weekly from REDCap into an Excel sheet. The CRC will use this information to call only valid prospects to complete a comprehensive confidential phone screen.

4.2 EMAIL SCREENING PROCEDURES

Individuals who message the UCSF Tobacco Coordinator email address or Facebook for more information about the study will receive an email asking them to complete a survey via REDCap. This survey will serve to determine their eligibility to attend an in-person screening visit.

Procedures for the email screen include the following:
• The CRC will respond and ask the participants to complete the REDCap Email Screening Survey. The REDCap Email Screening Survey has questions regarding the individual’s tobacco product use and health history, and that the expected length of the screen is approximately 10 minutes. Participants will fill this out themselves. Additionally, it contains a field for email addresses, so the CRC can connect participants via their email addresses to their responses.

• A report in the REDCap Database will generate a list of eligible participants.

• If eligible, the CRC will record the participants’ personal information in the Access Database. This includes their name, phone number, email address, date of birth, and address.

• Eligible participants may be contacted by phone or email if any follow-up clarification questions are needed.

• Eligible participants will be emailed 3 available appointment options from which they may choose to come in for an in-person screening visit. Participants will then respond with their desired appointment option, and will be scheduled for an in-person screening visit.
5 STUDY VISITS AND PROCEDURES

5.1 SCREENING VISIT

Participants will undergo a 1-2 hour in-person screening visit to determine study eligibility. During this visit, participants will complete a basic physical assessment: height, weight, heart rate, blood pressure, expired carbon monoxide, urine toxicology test, and pregnancy test (if applicable), saliva collection, and a Screening Packet containing questions regarding medical history and product use. Photographs of the participants’ e-cigarette and e-liquid will be taken.

The schedule of procedures for the screening visit will occur in the order as follows:

5.1.1 Consent Process

Upon initiation of the screening visit, the CRC will greet the participant and ask him/her to read the first line of the consent form aloud to confirm literacy. The CRC will instruct the participant to read each page of the consent document and initial at the bottom of each page indicating content understanding. The participant will be asked to refrain from signing the consent form until the CRC returns to discuss the consent form and answer any questions the participant may have regarding the study. The CRC will leave the room for approximately 10 minutes to allow the participant an adequate amount of time to read the consent form. The CRC will return, answer any questions, and present a brief PowerPoint presentation highlighting important aspects of the consent document. Consent will be obtained via participant and CRC signatures at the conclusion of the presentation. Three copies of the consent document will be signed and dated by both the participant and the CRC. The CRC should retain the initialed copy and the second copy, and the third copy will be given to the participant for their records. The participant will also be asked to read and given a copy of the Bill of Rights to ensure that the participant is aware of his/her rights in participating in a research study.

5.1.2 Urine Collection

After consent, the participant will be asked to provide a urine collection to test for drug use and pregnancy testing (if female).

If the participant has a positive toxicology screen (marijuana is okay), he/she will be dismissed and given the option to rescreen within 30 days.

The steps for the urine collection toxicology and pregnancy screenings are found in the “Urine Toxicology Screen SOP” and “Pregnancy Screen SOP.”

5.1.3 MILCOM

After confirming a negative toxicology screen and negative pregnancy screen, the participant will be asked to complete the MILCOM, a comprehensive Health History Questionnaire.

- Follow-up is required if any symptoms are endorsed on the MILCOM in the following Sections:
- Additional Illness or Problems
- Head and Neck
- Respiratory
- Cardiovascular
- Musculoskeletal
- Skin
- Neurological
- Mood

The CRC will follow up with the participant asking:
- How often and when was the last time you experienced these symptoms?
- Do you ever take medication for this? If so, how often?

Notes on the MILCOM follow-up will be recorded in empty space on the form.

5.1.4 Vital Assessment
The following physiological measures will be assessed:

- Height and Weight
- Blood pressure and heart rate
- Expired carbon monoxide (CO)

Steps for these assessments are found in the “Measuring Basic Vitals SOP” and “Measuring Expired CO Levels SOP.”

If the participant’s blood pressure is out of range, it will be re-tested at the end of the visit manually, following the saliva collection. If it is still out of range, they will be considered ineligible. If the participant’s expired CO levels are not ≥ 5 ppm, he/she will be dismissed from the visit and not paid.

5.1.5 Screening Packet
The screening packet will then be administered. It is broken into four main parts:

- **Section 1: Personal Data Form (Page 1)**
  - This section contains the participant’s contact information as well as an Emergency Contact.
- **Section 2: Demographics (Pages 2-3)**
  - This section contains information regarding the participant’s gender, age, ethnicity, race, and education.
- **Section 3: Use/History (Pages 4-18)**
  - This section contains information regarding participant’s use of nicotine replacement therapy, tobacco and e-cigarette product use, and drug/alcohol use.
- **Section 4: Medical History (Pages 19-23)**
  - This section contains information regarding the participant’s medical history, including exclusionary medical and psychiatric conditions.
If any symptoms are endorsed on the Medical History in Section 8, the CRC will follow up with the participant asking:

- How often and when was the last time you experienced these symptoms?
- Do you ever take medication for this? If so, how often?

Notes on the Medical History follow-up will be recorded at the bottom of the last page of the form (page 23).

The steps for administering and reviewing questionnaires are found in the “Administering Forms and Questionnaires SOP.”

### 5.1.6 Saliva Collection

After the participant completes the Screening Packet, he/she will be asked to provide a saliva collection. The steps for the saliva collection are found in the “Saliva Collection SOP.”

### 5.1.7 End of Screening Visit

At the end of the screening visit, the participant will be asked to fill out a “Certificate of Participation” in order to receive compensation for the screening visit. The participant will be dismissed and the CRC will inform him/her that he/she will be contacted in 1-2 weeks with eligibility results from the screening visit.

### 5.1.8 Post-Processing

The participant’s urine will be discarded and the CRC will store the participant’s saliva in the freezer at the UCSF Tobacco Research Center lab. The saliva samples will be labeled with the Study ID and transferred to the Benowitz Lab at the end of the day on Friday afternoons. The CRC will complete a Screening Log on the Shared Lab Drive filling in information on the samples dropped off. Cotinine results will be expected the following Tuesday.

The MILCOM will remain a source document and not entered into an electronic database. The CRC will complete the Screening Visit Log and enter data from the Screening Packet into the “SREC Screening Packet” REDCap database. Data entry should occur within 48 hours of the screening visit.

The CRC will submit the participant’s check request after confirming the participant’s smoking/vaping status (COT ≥ 50 ng/ml). If the participant’s cotinine is < 50 ng/ml, they will not be compensated for their screening visit.

### 5.2 Preparation for Inpatient Portion

#### 5.2.1 Product Purchasing

The CRC will purchase the participant’s TC products from local smoke shops using a petty cash fund. The CRC will purchase enough products to be used for the participant’s 4 outpatient days, inpatient study days, and for lab analysis. In order to determine total TC products, the CRC will refer to the Screening Packet, Section 3:
Tobacco Smoking History, question #8 for cigarettes per day. The SREC devices will be obtained through NIDA.

5.2.2 5B SETUP PAPERWORK
After study dates have been confirmed with the participant and the research ward, an admission request will be submitted via secure email to the research ward. The CRC will then prepare CTSI-5B Set-up paperwork for the admissions.

The set-up paperwork consists of the following:

5.2.2.a Coversheet
- The coversheet contains general information regarding the study and supplies needed.
- CRC will place a label with the participant’s name and study ID, and edit the admission and set-up drop-off dates.

5.2.2.b Consent Form
- An original signed copy of the consent form from the Screening Visit will be included in the set-up.

5.2.2.c Nurses Flow Sheet
- The Nurses Flow Sheet contains study procedures and time points for each day of the inpatient admission.
- CRC will update this form with participant’s TC product brands or SREC assignment.

5.2.2.d Outpatient Form
- The outpatient form has PHI filled out by the participant at the screening visit with name, SSN, date of birth, and contact information.

5.2.2.e MD Orders
- The MD Orders are pre-signed by the Study Physician that will conduct the physical during the admissions.
- CRC will write in the admission date and pencil in the participant’s name on the top right corner.

5.2.2.f Admit PE
- The Admit PE will be filled out by the Study Physician as they perform the history and physical.
- CRC will pencil in participant’s name in the top right corner.

5.2.2.g Adverse Event Form
- The Adverse Event form is included in the set-up should any adverse events occur during the course of the study.
- CRC will change the study ID.
5.3 ORIENTATION

Participants will attend an Orientation Visit on a Thursday, to begin their Outpatient Days in Study Block #1. This visit will last approximately 1 hour. During the Orientation Visit, study procedures will be described in detail again. The following will take place:

5.3.1 Product Assignment
The CRC will input the participant’s initials, product assignment, and date he/she is assigned to that condition into the “Product Assignment Tracking Log”. Product assignment procedures are described in Section 2.4.2.

5.3.2 Distribution of Study Products
Participants will be given SREC or TC products (based on assignment schedule) to use for the 4 outpatient days prior to their admission to the CTSI-5B research ward. Before distribution, the CRC will weigh all of the products. Participants will sign a product accountability form and be instructed to return all empty and unused products at the end of their outpatient period.

5.3.3 Product Use Diary
Participants will be asked to keep track of their product use during their outpatient days. Instructions for using a mobile app (ex: Nomie 2 app) or paper log will be reviewed at the Orientation Visit to track product use.

In addition to tracking when they begin a smoking/vaping session, the Product Use Diary will also include tracking the volume of e-liquid used and TC smoked per day.

The Product Use Diary – paper log version – will be turned into the CRC during admission. If using the mobile app, participants will email the final report to the secure UCSF Tobacco Coordinator email address at the end of the day, after their last vaping/smoking sessions.

To note, the Nomie 2 app is a mobile application used to track time. It is not advertised nor is it considered to be a healthcare app.

5.3.4 Urine Collection
Participants will provide a urine collection to be tested for nicotine by-products. This urine collection will amount to 40mL. The CRC will adjust the urine pH, label, and store the urine in the UCSF Tobacco Research Center lab. The steps for adjusting the urine pH are found in the “Adjusting Urine pH SOP.”

5.4 STUDY BLOCK #1

5.4.1 Outpatient Days
After the Orientation Visit, participants will begin their 4 outpatient days and use the product assigned at randomization. They will track their product use with a smartphone diary application or paper log, recording every time they start/stop a TC or SREC session. After they have completed their use for the day, they will email
the summary report to the CRC or the CRC will collect the paper logs at admission. If participants have not emailed their summaries by the following morning, the CRC will send them a reminder email.

5.4.2 Admission & Inpatient Days
After the 4 outpatient days, participants will check into the Zuckerberg San Francisco General Hospital Clinical Research Center on the morning of Study Block #1, Day #5 at approximately 7am. As required for all hospital admissions, participants will have a medical history and physical examination conducted by the Study Physician.

On **Day #5** (Hospital Day 1) of the study block week, the following will occur:

- The participant will be asked to arrive at the research ward at 7am to begin their inpatient study days. They will be given a light breakfast and, if they normally drink caffeinated beverages, they will be allowed a cup of their usual beverage (e.g., coffee or tea).
- At approximately 8am, a plastic catheter (thin flexible tube) will be inserted into a vein on one of the forearms (this will be used to withdraw multiple blood samples and will be kept in place for about 10 hours).
- At approximately 9:00am, the participant will be asked to smoke a commercial cigarette or the SREC device and to take puffs only at times signaled by the voice recorder.
- For the SREC device: After each puff of the standardized session, we will capture the aerosol (or vapor) the participant breathes out by asking them to exhale into a sterile polypropylene mouthpiece which is connected to 3 gas traps. The gas traps are connected in series (i.e. in a line) and contain diluted hydrochloric acid or a solution containing citric acid, sodium phosphate, and ascorbic acid. A vacuum pump connected to the traps will suck the exhaled aerosol into the traps. There will be NO contact between the mouth or body with the diluted acidic solution in the gas traps. This step will allow us to compute the dose of nicotine taken in from the e-cigarette during the standardized session.
- The participant will not be allowed to smoke/vape again until 4 hours later, at which time they will be given one of their usual brand of cigarette or the SREC device and allowed to smoke/vape it in their usual way.
- Blood samples, about one teaspoon each, will be withdrawn just before smoking/vaping, and during the 4-hour abstinence period at 2, 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after smoking/vaping.
- They will be asked to fill out several Questionnaires about their smoking experience before and after using the product and during the 4 hours when they are not smoking/vaping.

On **Day #6** (Hospital Day 2) of the study block week, the following will occur:

- The participant will be able to smoke their cigarettes or use the SREC device as they wish from 8am to 12am midnight.
• The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
• The participant will wear a 24-hour ambulatory blood pressure and heart rate recorder for cardiovascular monitoring.
• The participant will be asked to fill out several Questionnaires.
• At 12 noon, a single blood sample will be taken.
• There will also be 24-hour urine collections.

On **Day #7** (Hospital Day 3) of the study block week, the following will occur:

• In the morning, an intravenous catheter (like on Day #5) will be placed for blood collections every four hours from 8am to midnight, and at 8am the next day.
• The participant will continue to be able to smoke their cigarettes or use the SREC device as they wish.
• The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
• The participant will be asked to fill out several Questionnaires.
• There will also be 24-hour urine collections.

### 5.5 STUDY BLOCK #2

#### 5.5.1 Outpatient Days

After being discharged from the research ward, the participant will be able to use the SREC device or tobacco cigarette product as they wish for 4 days. They will be asked to use only use the provided product during these outpatient days and will keep track of product usage with the product use diary.

#### 5.5.2 Admission & Inpatient Days

The second inpatient admission will follow the same structure as the first inpatient admission mentioned above, but instead the participant will be using the alternate product.

### 5.6 STUDY BLOCK #3

#### 5.6.1 Outpatient Days

After being discharged from the research ward, the participant will be able to use both the SREC device AND their tobacco cigarette product as they wish for 4 days. The participant will only use the provided products during these outpatient days and will keep track of their product usage with the study diary.

#### 5.6.2 Admission & Inpatient Days

The participant will be admitted one last time for 3 more days.

On **Day #5** (Hospital Day 1) of this last study block week, the following will occur:
• The participant will be asked to arrive at the research ward at 7am to begin the
inpatient study days. Light breakfast will be given and caffeinated beverages are
allowed.
• At approximately 8am, the participant will be asked to use the SREC device in a
standardized session similar to the other inpatient days and to take puffs only at
times signaled by the voice recorder.
• The standardized SREC session will repeat again every 90 minutes for a total of 8
sessions.
• Between the standardized SREC sessions, the participants are allowed to use
their own tobacco cigarettes or the SREC device as often as they’d like.
• The time of each cigarette or SREC puff will be recorded using a smartphone
diary application or paper log and all cigarette butts and SREC devices will be
collected at the end of the day to determine product usage.

On **Day #6** (Hospital Day 2) of this last study block week, the following will occur:

• At approximately 8am, the participant will be asked to use the SREC device in a
standardized session similar to the other inpatient days and to take puffs only at
times signaled by the voice recorder.
• The participant will be asked to use the SREC device again every 90 minutes for
a total of 8 sessions.
• Between the standardized SREC sessions, the participant is allowed to use their
own tobacco cigarettes or the SREC device as often as they’d like.
• The time of each cigarette or SREC puff will be recorded using a smartphone
diary application or paper log and all cigarette butts and SREC devices will be
collected at the end of the day to determine product usage.
• The participant will wear a 24-hour ambulatory blood pressure and heart rate
recorder for cardiovascular monitoring.
• The participant will be asked to fill out several Questionnaires.
• At 12 noon, a single blood sample will be taken.
• There will also be 24-hour urine collections.

On **Day #7** (Hospital Day 3) of this last study block, the following will occur:

• In the morning, an intravenous catheter (like on the other study blocks) will be
placed for blood collections every four hours from 8am to midnight, and at 8am
the next day.
• At approximately 8am, the participant will be asked to use the SREC device in a
standardized session similar to the other inpatient days and to take puffs only at
times signaled by the voice recorder.
• The participant will be asked to use the SREC device again every 90 minutes for
a total of 8 sessions.
• Between the standardized SREC sessions, the participant is allowed to use their
own tobacco cigarettes or the SREC device as often as they’d like.
• The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
• The participant will be asked to fill out several Questionnaires.
• There will also be 24-hour urine collections.
• Participation will be complete once the participant is discharged from the hospital the next morning.

5.7 PARTICIPANT COMPENSATION

Participants will be compensated according to Table 2:

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Screening Visit</th>
<th>Study Block #1</th>
<th>Study Block #2</th>
<th>Study Block #3</th>
<th>Completion Bonus</th>
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<tr>
<td>Compensation</td>
<td>$20*</td>
<td>$660</td>
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<td>Total Compensation</td>
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<td></td>
<td></td>
<td></td>
<td>$2500</td>
</tr>
</tbody>
</table>

*Compensation for the screening visit will be contingent upon a negative toxicology drug screen (THC is okay) and a cotinine of ≥ 50 ng/ml.

Compensation for participants who drop-out and do not make it through all portions of the study is described in Section 2.5.2.
6 ADVERSE EVENTS AND PROTOCOL DEVIATIONS

6.1 SAFETY MONITORING
During the inpatient stay, participants will be monitored by the CRC and the nursing staff who will directly contact the Study Physician in case of any subsequent adverse events. If the participants experience adverse effects, the Study Physician will evaluate this with them and decide if they should be withdrawn from this study.

6.2 REPORTING ADVERSE EVENTS
Reporting of serious adverse events will follow the current requirements of the UCSF Human Research Protection Program’s Institutional Review Board (IRB), with the concurrent reporting to the Nurse Manager at the CRC. Specifically, the following will be reported within five (5) working days of the Principal Investigator’s (PI) awareness, in writing:

- All serious adverse events associated with the study procedures and/or
- Any incidents or problems involving the conduct of the study or patient participation, including problems with the recruitment and/or consent process. The PI will provide a discussion of such events to the CHR on an annual basis during study renewal.
- Any incidents or questionable adverse events are discussed at the weekly staff meetings with the PI.

The standard adverse event grading scale will be used to report any potential adverse events from phlebotomy, study drug, or other study procedures:

- **Grade 1 - Mild AE**: did not require treatment
- **Grade 2 - Moderate AE**: resolved with treatment
- **Grade 3 - Severe AE**: resulted in inability to carry on normal activities and required professional medical attention
- **Grade 4 - Life-threatening or disabling AE**
- **Grade 5 - Fatal AE**

The supervising Study Physician will be notified of all Grades 2 through 5 AEs. Additionally, the PI will be notified of all Grades 4 and 5 AEs. Grades 3 through 5 AEs will be reported to the CCRC and the CHR. Grades 4 and 5 will be reported within 24 hours. Grade 3 will be reported within 20 days. Grade 2 will be included in the yearly progress report. Grade 1 will not be reported.

6.3 PROTOCOL DEVIATIONS & VIOLATIONS
Protocol deviations are defined as an event that deviates from the defined study protocol, but does not pose any risk to the participant or harm to the quality of the study data. For example, a follow-up call may be conducted outside of the stipulated window, or a section of questions on a questionnaire may be missed due to a mistake in branching. Deviations will be recorded on a protocol deviation sheet and reviewed and signed by the PI.
Protocol violations are events that deviate from the defined study protocol, but put the participant at risk and/or cause harm to the study data. Protocol violations will be recorded on a protocol violation sheet, reviewed and signed by the PI and reported to the CHR.
7 DATA COLLECTION AND MANAGEMENT

7.1 DATA COLLECTION FORMS
All of the following measures will be collected.

Screening Process:
- UCSF Tobacco Research Center REDCap Screen

In-Person Screening Visit:
- MILCOM
- Screening Packet
- Wisconsin Inventory of Smoking Dependence Motives (WISDM)
- Nicotine Dependence Syndrome Scale (NDSS)
- Center for Epidemiologic Studies Depression Scale (CES-D)

Inpatient Study Visits:
- Day 5, Block 1 & 2 & 3:
  - Questionnaire of Smoking Urges (QSU) or modified for E-Cigarettes
  - Cigarette Evaluation Scale (mCES) or modified for E-Cigarettes
  - Positive and Negative Affect Scale (PANAS)
  - Minnesota Behavioral Scale (MNWS)
- Day 6, Block 1 & 2 & 3:
  - Questionnaire of Smoking Urges (QSU) or modified for E-Cigarettes
  - Cigarette Evaluation Scale (mCES) or modified for E-Cigarettes
  - Positive and Negative Affect Scale (PANAS)
  - Minnesota Behavioral Scale (MNWS)
- Day 7, Block 1 & 2 & 3:
  - Questionnaire of Smoking Urges (QSU) or modified for E-Cigarettes
  - Cigarette Evaluation Scale (mCES) or modified for E-Cigarettes
  - Positive and Negative Affect Scale (PANAS)
  - Minnesota Behavioral Scale (MNWS)

Information on how data is stored, processed and analyzed can be found in the Data Safety and Monitoring Plan.
8 STATISTICAL ANALYSIS PLAN

8.1 DATA ANALYSIS

Statistical analysis of the data from the crossover studies will be conducted using the standard procedures for such designs. Means of the outcome measures (nicotine intake measures, heart rate, blood pressure, acrolein metabolite excretion, epinephrine excretion, etc.) will be tested for equality using a repeated measures model. Tests will include, in addition to treatment condition, a test for order to determine possible carry-over effects. Estimation will be done using full-information maximum likelihood methods so that we can use all data in estimation even if some is missing (although based on prior work we expect almost none). For some of our research questions the data will be descriptive and will not address specific hypotheses because the work is novel and little is known about the questions. For these, standard summary statistics, including measures of variation, will be used.

Study Objective #1: Nicotine delivery, systemic exposure, and effects of SREC vs TC

1. In the standardized use session, we will determine the plasma nicotine peak concentration, time to peak concentration and 240 minute area under plasma nicotine concentration-time curve (AUC) and compare SREC to TC. We will use ratios of values for the two products, as is commonly done in comparing the pharmacokinetics of different pharmaceutical products. The ratio of AUCs will give us information on relative doses obtained from SREC and TC.

2. Systemic exposure to nicotine from daily use two ways. In one approach we will compute the 24-hr plasma nicotine AUC during ad libitum SREC use and then use population nicotine clearance estimates and the AUC to estimate an absolute systemic dose of nicotine (as we have done previously with reduced nicotine content cigarettes). In another approach we will use TNE measured in the 24 hour inpatient urine samples, since TNE accounts for more than 90% of excreted nicotine and thus is a useful estimate of daily nicotine intake. Each method of estimating daily nicotine intake has its limitations. By using two measures of nicotine exposure we can be confident of the highest quality of our estimates. We will compute ratios of 24-hr AUCs or 24 TNEs for SREC/TC and for dual use/TC, which will be statistically compared against a value of 1.0 using a t-test against a constant. These ratios can be viewed as measures of titration of nicotine intake. If subjects titrate perfectly, the ratio will be 1.0. We will also examine the idea of partial titration – that is, some but less than complete titration (as opposed to no relationship between intake from SREC and TC at all). We will do so by examining the correlations across subjects of nicotine AUC from SREC vs TC, and dual use vs TC.
The finding of a significant correlation would suggest that even if titration is incomplete, smokers who take in more nicotine from TC will also take in more nicotine from SREC or from dual use.

3. To explore the relationship of nicotine intake to satisfaction, psychological reward and withdrawal symptoms, we will compare average measures from the mCEQ, the QSU and the MNWS for outpatient days and separately during inpatient days for the SREC, TC and dual use conditions. As an exploratory analysis, using the standard methods for a two-arm crossover design (including testing for carryover effects) we will test whether differences in subjective effects are related to difference in nicotine intake. For example, we may find that nicotine levels while using SREC or dual use are lower than when using TC, but that there is no difference in withdrawal symptoms or satisfaction, thus suggesting that the sensory aspects of puffing behavior per se are rewarding.

4. The patterns of SREC puffing and TC use will be examined looking at the average and variability (SD) of inter-puff or inter-cigarette interval and the fraction of total daily units consumed in each of four 4-hour intervals throughout the day. As an exploratory analysis, we will compare patterns of use (average inter-puff interval, a measure of clustering: patterns of morning vs evening vs regular throughout the day use) to total nicotine intake and dependence measures, and will compare use patterns for SREC vs TC. For example, we might expect to find that smokers who cluster their TC smoking (i.e. in the morning or evening) will cluster their SREC use the same way, while those who smoke TC regularly throughout the day will similarly use SREC continuously. On the other hand if such trends are not observed it would raise interesting questions about the nature and differences of nicotine reward and reinforcement from the different modalities.

**Study Objective #2: Safety of SREC use**

5. Using paired t test, with log transformation of analytic concentrations, which are known not to be normally distributed, we will compare biomarkers of toxicant exposure for SREC alone vs TC alone use: urine excretion of mercapturic acid metabolites of VOCs, with a particular focus on acrolein, propylene oxide and benzene; PAHs metabolites and minor tobacco alkaloids (anabasine, anatabine, nicotelline). These compounds have relatively short half-lives and will be at steady state within a few days. We will also compare excretion of NNAL, the metabolite of the tobacco specific nitrosamine NNK. This has a longer half-life (10-16 hr) and will not regain steady state in a few days. However, in other short term studies of water pipe (hookah) use we have seen substantial changes in NNAL, providing us with some information as to relative exposures. We will compare the 24 hr urines obtained in the hospital under controlled
conditions (where we are confident that there is no use of other products or SHS exposure) for SREC-only vs TC-only use.

6. Analysis of the CV effects of EC use will include two measures that we have found in prior studies to be most sensitive to nicotine: heart rate acceleration and urine epinephrine excretion. On Day 6 we will determine 24 hour average heart rate, daytime heart rate (8 AM to 10 PM), and nighttime heart rate (10 PM to 8 AM). We have found previously that nicotine exposure affects daytime heart rate more than at nighttime. We will also measure ambulatory blood pressure on Day 6 of each block. Our prior research using similar methods has shown differences in circadian blood pressure patterns with cigarettes vs nasal spray. Urine epinephrine excretion will be examined in 24 hour urines. These CV measures, as well as blood and urine biomarkers of platelet activation, oxidant stress, endothelial dysfunction and inflammation will be compared between SREC and TC by paired t tested, with log transformation of measures as appropriate.

**Study Objective #3: Harm Reduction with dual use of SREC and TC**

7-9. The comparison of nicotine and toxicant exposure, subjective and CV effects of dual TC/use compared to TC is a major objective of this project. It is this comparison that informs the question of harm reduction. The data analyses will be similar to those described for study objectives #1 and #2 above, except in objective #3 the comparisons with be between dual SREC/TC use and TC alone use.

**Study Objective #4: Biomarkers to distinguish TC from SREC use**

10. We expect that we will be able to distinguish SREC vs TC use from differential exposure to nicotine vs other tobacco constituents. Specifically we propose that nicotelline (which we predict will have much higher levels in TC smoke than in SREC emissions), when measured in urine and normalized for nicotine intake (that is, the nicotelline/cotinine or nicotelline/TNE ratio) will distinguish TC smoking from SREC use. This study will allow us to determine the sensitivity and specificity of biomarkers to distinguish the two. We will do the same analysis for anabasine and anatabine. Once we establish the range of urine nicotelline/cotinine or anabasine/cotinine ratios during exclusive TC and EC use, we anticipate being able to estimate in a dual user what fraction of nicotine is derived from TC vs EC, which will be validate using relative exposures to tobacco smoke VOCs.

**8.2 ANALYTICAL CHEMISTRY**

*Nicotine and Cotinine:* Concentrations of nicotine and cotinine in plasma are determined using gas chromatography (GC) with nitrogen-phosphorus (N-P) detection, modified for
use with a capillary column. Lower limits of quantitation (LLOQs) for nicotine and cotinine are 1 and 10 ng/mL respectively.

**Simultaneous Determination of Multiple Nicotine Metabolites in Urine (Total Nicotine Equivalents/TNE):** Concentrations of nicotine and its major metabolites (nicotine, cotinine and trans-3’-hydroxycotinine and their glucuronides; nicotine-1’-N-oxide, nornicotine, norcotinine, cotinine-N-oxide) are measured by LC-MS/MS. The method is similar to our published method for cotinine and 3HC, with modifications in the HPLC separation and mass spectrometer parameters for the multiple analytes. LLOQs range from 2 to 10 ng/mL.

**TSNAs:** Urine concentrations of NNAL are determined using LC-MS/MS with LLOQ of 0.25 pg/mL.

**Mercapturic Acid Metabolites of VOCs** (acrolein, propylene oxide, ethylene oxide, acrylonitrile, 1,3-butadiene, acrylamide and benzene): The metabolites are extracted from urine and converted to pentafluorobenzyl ester derivatives to enhance sensitivity of detection. The analysis is by LC-MS/MS with LLOQs ranging from 0.1 to 5 ng/mL.

**Phenolic metabolites of polycyclic aromatic hydrocarbons** (naphthalene, fluorene, phenanthrene and pyrene) will be determined by LC-MS/SM with LLOQ of 0.01 to 0.05 ng/ml.

**Minor tobacco alkaloids:** Concentrations of anabasine and anatabine in urine are determined by LC-MS/MS using a procedure similar to the method for Simultaneous Determination of Multiple Nicotine Metabolites described above, with modifications in the HPLC separation and mass spectrometer parameters for these two analytes. The LLOQs are 0.5 ng/mL. Concentrations of nicotelline (LLOQ 4 pg/mL) are determined by a published method.(30) For analysis of e-liquids, samples will be diluted and analyzed by LC-MS for nicotine, minor tobacco alkaloids, and TSNA by a published method.

**Cardiovascular Biomarkers:** Assays will be done by commercial or academic laboratories. Urine epinephrine is measured by Quest Laboratories by HPLC. Urinary F2-isoprostanes and 11-dehydro thromboxane B2 will be measured by LC-MS/MS by Dr. James Zhang at Duke University. Vascular endothelial growth factor (VEGF), intercellular adhesion molecule 1 (s-ICAM-1), interleukin -6 (IL-6) will be measured by the clinical laboratory at Zuckerberg San Francisco General using immunoassay methods.
9 DUTIES AND RESPONSIBILITIES OF STAFF

9.1 PRINCIPAL INVESTIGATOR
The Principal Investigator is responsible for study design and oversight of implementation, data analysis, and manuscript preparation.

9.2 CO-PRINCIPAL INVESTIGATORS
The Co-Principal Investigators are responsible for study design and oversight of implementation, data analysis, and manuscript preparation, with the assistance of the Principal Investigator.

9.3 STUDY PHYSICIAN
The Study Physician is responsible for medical study chart review and eligibility determination, medical history and physical examination at SFGH admissions, and other medically related expertise.

9.4 PROJECT MANAGER
The Project Manager is responsible for overall functioning of study coordination with CHR protocols; monitoring of study budget and coordination with departmental administrative personnel; supervision of research associates; management of clinic facilities.

9.5 CLINICAL RESEARCH COORDINATOR
The CRC will oversee study logistics including consenting and screening participants, conducting study visit procedures, coordinating inpatient admissions and procedures with nursing staff at the research ward, coordinating specimen testing with laboratory, overseeing participant reimbursement, maintaining study charts and data entry.
## 10 UCSF INSTITUTIONAL REVIEW BOARD (IRB)

### Laurel Heights Committee - Updated November 2017

FWA #00000068, IRB Registration #00003471

<table>
<thead>
<tr>
<th>Member's Name &amp; Degree</th>
<th>Department - Division - Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair: Reese T. Jones, MD <a href="mailto:reese.jones@ucsf.edu">reese.jones@ucsf.edu</a></td>
<td>Psychiatry - UCSF</td>
</tr>
<tr>
<td>Vice Chair: Patricia Katz, PhD <a href="mailto:patti.katz@ucsf.edu">patti.katz@ucsf.edu</a></td>
<td>Medicine – Rheumatology/Arthritis - UCSF</td>
</tr>
<tr>
<td>Vice Chair: Diane W. Wara, MD <a href="mailto:warad@peds.ucsf.edu">warad@peds.ucsf.edu</a></td>
<td>Pediatrics - Pediatric Immunology/ Rheumatology - UCSF</td>
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VAMC Human Studies Coordinator
11 APPENDIX

11.1 CONSENT FORM

NAME:
DOB:
MRN#:

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: “Cigarette Harm Reduction with Scheduled Electronic Cigarette Use”

This is a research study about 

nicotine exposure and safety of electronic cigarettes. The study researcher, Dr. Neal Benowitz, MD from the University of California, San Francisco

Department of Medicine, is conducting this study and the Clinical Research Coordinator will explain this study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating, and discuss your decision with your family or friends if you wish. If you have any questions, you may ask the researchers.

You are being asked to take part in this study because you are a healthy smoker who smokes at least 5 cigarettes every day and has had experience using an electronic cigarette (e-cigarette) device.

Why is this study being done?

The purpose of this study is to learn more about nicotine exposure and safety of e-cigarettes, assessing key pharmacological factors associated with the potential addictiveness and health effects of these products.

Standardized Research E-Cigarettes, provided by the National Institutes of Health, will be used in this study and are considered experimental by the Food and Drug Administration and cannot be used outside of research studies.

This study is funded by the National Institutes of Health (NIH).

How many people will take part in this study?

About 20 people will take part in this study at UCSF.

What will happen if I take part in this research study?

If you agree, the following procedures will occur:

Screening Visit: This is an approximately 2 hour screening visit to see if you want to be in the study, and to see if you meet the qualifications to be in the study. You will first read this consent and ask any questions you wish. After reading the consent, you must sign it to continue the screening visit in order to be considered for participation in the study.
The following happens at this screening visit:

- **Forms:** You will be asked to fill out forms to provide information about yourself (including age, racial/ethnic background, medical and social history, use of prescription and over-the-counter medications, and the use of tobacco, alcohol, caffeine, and recreational drugs). In addition, there are several forms specifically about your smoking behavior, history, and dependence on nicotine.
- **Physical Data:** Your height, weight, heart rate, and blood pressure will be collected.
- **Saliva Sample:** You will be asked to give a saliva sample for laboratory tests to confirm that you are a smoker.
- **Expired Carbon Monoxide (Expired CO):** You will be asked to breathe into a machine that records how much carbon monoxide is present in your lungs, in order to confirm your smoking status. If the testing indicates that you are not a smoker, you will be considered ineligible and dismissed without payment.
- **Urine Sample:** A sample of your urine will be collected for:
  - **Drugs Testing**
    - If the results are positive for substances other than marijuana or prescribed drugs, you will not be eligible to participate in the study. You will be dismissed without compensation, and your urine will be discarded. However, if you would like to rescreen for the study at a later time (within 30 days), we will give you the option to schedule another screening visit. Results must be negative at that time for you to receive compensation for the visit and continue in the study if otherwise eligible.
    - If the results are positive for marijuana, you may be continued to be evaluated for eligibility.
    - If the results are positive for prescribed drugs, you may be continued to be evaluated for eligibility.
  - **Pregnancy Testing (if applicable)**
    - If the results are positive for pregnancy, you will not be eligible to participate in the study. You will be compensated for the screening visit and your urine will be discarded.

If the screening exam shows that you can be in the main part of the study and you choose to continue, this is what will happen next:

**Orientation Visit:** Once your smoking status is confirmed from the screening visit saliva sample, if eligible, you will be asked to come back to the UCSF Tobacco Research Center for an Orientation Visit.

At this visit, we will prepare you for Study Block #1.

- We will ask you **not to use any marijuana or other recreational drugs from the today until the study is completed.**
- A computer generated program will assign you to one of two products—e-cigarette only or tobacco cigarette only for the first week of the study (Block #1), then the alternate product for the following week (Block #2).
• We will purchase your normally used tobacco cigarette products or provide you with Standardized Research E-Cigarettes (SREC), and give you to use for 4 days (outpatient days) prior to your admission to the research ward.

• You will also be given a study diary (smartphone app or paper) to track your product use (e.g., volume of e-liquid used and tobacco cigarettes smoked per day) and will record each evening an assessment of urges to smoke and nicotine withdrawal symptoms experienced throughout the day. You will also be asked to return all electronic cigarette products and tobacco cigarette butts so that we may assess the amount of nicotine consumed and tobacco burned.

• Urine Collection: A sample of your urine will be collected for and tested for nicotine breakdown by-products.

The Standardized Research E-Cigarette, or SREC, was developed by the National Institute of Drug Abuse (part of the NIH) to help researchers assess uncertainties in electronic nicotine delivery devices. You will be provided a handout that describes the SREC device, including its tank and battery characteristics, description of its use, and the composition of the e-liquid ingredients. The SREC devices are considered experimental by the Food and Drug Administration and cannot be used outside of research studies.

Study Block #1 Outpatient Procedures:
You will be able to use your SREC or tobacco cigarette product as you wish for 4 days. We will ask that you use only the provided product during these outpatient days and that you keep track of your product usage with the study diary given to you at Orientation. You will be asked to abstain from smoking the night before your admission to the hospital starting at 10:00pm.

Study Block #1 Inpatient Procedures: You will be admitted to the ZSFG Clinical & Translational Science Institute (CTSI) clinical research site (CRS) as an inpatient for 3 days.

During the admission, you will have a pregnancy test (if female), medical history and physical examination conducted by the Study Physician or a Nurse Practitioner. This is required for all hospital admissions and these documents will become part of your permanent ZSFG medical record. If you wish, the results of your physical examination will be shared with you by the health care provider.

On Day #5 (Hospital Day 1) of the study block week, the following will occur:
1. You will be asked to arrive at the research ward at 7am to begin your inpatient study days. You will be given a light breakfast and, if you normally drink caffeinated beverages, you will be allowed a cup of your usual beverage (e.g., coffee or tea).
2. At approximately 8am, a plastic catheter (shin flexible tube) will be inserted into a vein on one of your forearms (this will be used to withdraw multiple blood samples and will be kept in place for about 10 hours).
3. At approximately 9:00am, you will be asked to smoke a commercial cigarette or the SREC device and to take puffs only at times signaled by the voice recorder.
4. For the SREC device. After each puff of the standardized session, we will capture the aerosol (or vapor) you breathe out by asking you to exhale into a sterile polypropylene mouthpiece which is connected to 3 gas traps. The gas traps are connected in series (i.e. in a line) and contain diluted hydrochloric acid or a solution containing citric acid.
sodium phosphate, and ascorbic acid. A vacuum pump connected to the traps will suck your exhaled aerosol into the traps. There will be NO contact between your mouth or body with the diluted acidic solution in the gas traps. This step will allow us to compute the dose of nicotine taken in from the e-cigarette during the standardized session.

5. You will not be allowed to smoke/vape again until 4 hours later, at which time you will be given one of your usual brand of cigarette or the SREC device and allowed to smoke/vape it in your usual way.

6. Blood samples, about one teaspoon each, will be withdrawn just before smoking/vaping, and during the 4-hour abstinence period at 2, 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after smoking/vaping.

7. You will be asked to fill out several Questionnaires about your smoking experience before and after using the product and during the 4 hours when you are not smoking/vaping.

On Day #6 (Hospital Day 2) of the study block week, the following will occur:

1. You will be able to smoke your cigarettes or use the SREC device as you wish from 8am to 12am midnight.
2. The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
3. You will wear a 24-hour ambulatory blood pressure and heart rate recorder for cardiovascular monitoring.
4. You will be asked to fill out several Questionnaires.
5. At 12 noon, a single blood sample will be taken.
6. There will also be 24-hour urine collections.

On Day #7 (Hospital Day 3) of the study block week, the following will occur:

1. In the morning, an intravenous catheter (like on Day #5) will be placed for blood collections every four hours from 8am to midnight, and at 8am the next day.
2. You will continue to be able to smoke your cigarettes or use the SREC device as you wish.
3. The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
4. You will be asked to fill out several Questionnaires.
5. There will also be 24-hour urine collections.

Study Block #2 Outpatient Procedures:
After being discharged from the research ward, you will be able to use the SREC device or tobacco cigarette product as you wish for 4 days. We will ask that you only use the provided product during these outpatient days and that you keep track of your product usage with the study diary.

Study Block #2 Inpatient Procedures:
Your second inpatient admission will follow the same structure as the first inpatient admission mentioned above, but instead you will be using the alternate product.
Study Block #3 Outpatient Procedures:
After being discharged from the research ward, you will be able to use both the SREC device AND your tobacco cigarette product as you wish for 4 days. We will ask that you only use the provided products during these outpatient days and that you keep track of your product usage with the study diary.

Study Block #3 Inpatient Procedures: You will be admitted one last time to the ZSFG CTSI-CRS as an inpatient for 3 more days.

On Day #5 (Hospital Day 1) of this last study block week, the following will occur:
1. You will be asked to arrive at the research ward at 7am to begin your inpatient study days. You will be given a light breakfast and, if you normally drink caffeinated beverages, you will be allowed a cup of your usual beverage (e.g., coffee or tea).
2. At approximately 8am, you will be asked to use the SREC device in a standardized session similar to the other inpatient days and to take puffs only at times signaled by the voice recorder.
3. You will be asked to use the SREC device again every 90 minutes for a total of 8 sessions.
4. Between the standardized SREC sessions, you are allowed to use your own tobacco cigarettes or the SREC device as often as you’d like.
5. The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.

On Day #6 (Hospital Day 2) of this last study block week, the following will occur:
1. At approximately 8am, you will be asked to use the SREC device in a standardized session similar to the other inpatient days and to take puffs only at times signaled by the voice recorder.
2. You will be asked to use the SREC device again every 90 minutes for a total of 8 sessions.
3. Between the standardized SREC sessions, you are allowed to use your own tobacco cigarettes or the SREC device as often as you’d like.
4. The time of each cigarette or SREC puff will be recorded using a smartphone diary application or paper log and all cigarette butts and SREC devices will be collected at the end of the day to determine product usage.
5. You will wear a 24-hour ambulatory blood pressure and heart rate recorder for cardiovascular monitoring.
6. You will be asked to fill out several Questionnaires.
7. At 12 noon, a single blood sample will be taken.
8. There will also be 24-hour urine collections.

On Day #7 (Hospital Day 3) of this last study block (the last day!), the following will occur:
1. In the morning, an intravenous catheter (like on the other study blocks) will be placed for blood collections every four hours from 8am to midnight and at 8am the next day.
2. At approximately 8am, you will be asked to use the SREC device in a standardized session similar to the other inpatient days and to take puffs only at times signaled by the voice recorder.

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3. You will be asked to use the SREC device again every 90 minutes for a total of 8
   sessions.
4. Between the standardized SREC sessions, you are allowed to use your own tobacco
   cigarettes or the SREC device as often as you'd like.
5. The time of each cigarette or SREC puff will be recorded using a smartphone diary
   application or paper log and all cigarette butts and SREC devices will be collected at the
   end of the day to determine product usage.
6. You will be asked to fill out several Questionnaires.
7. There will also be 24-hour urine collections.
8. Your participation will be complete when you are discharged from the hospital the next
   morning.

Study Schedule:

| Study Block Week #1: SREC-only or cigarette only (computer randomized) |
| --- | --- | --- | --- | --- | --- | --- |
| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| Thurs | Fri | Sat | Sun | MONDAY | TUESDAY | WEDNESDAY |
| < -- At Home -- > | < < Hospital > > |
| SREC/Usual product use as regular | Daily Diary | Standardized Session | 4-hr abstinence and blood draws | Followed by Free use | Free use | 24-hr BP/HR monitoring |
| | | | | | | 1 blood draw |
| | | | | | | 24-hr urine collection |
| | | | | | | Free use |
| | | | | | | Circadian blood draws |
| Study Block Week #2: Alternate Product from Week #1 |

| Study Block Week #2: Alternate Product from Week #1 |
| --- | --- | --- | --- | --- | --- | --- |
| Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| Thurs | Fri | Sat | Sun | MONDAY | TUESDAY | WEDNESDAY |
| < -- At Home -- > | < < Hospital > > |
| Discharged from the hospital Thursday morning | SREC/Usual product use as regular | Standardized Session | 4-hr abstinence and blood draws | Followed by Free use | Free use | 24-hr BP/HR monitoring |
| Daily Diary | | | | | | 1 blood draw |
| | | | | | | 24-hr urine collection |
| | | | | | | Free use |
| | | | | | | Circadian blood draws |
Study Block Week #3: Standardized SREC Use & Free Use of both products

Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7
-----|-------|-------|-------|-------|-------|-------
Thurs | Fri   | Sat   | Sun   | MONDAY | TUESDAY | WEDNESDAY
< At Home > | < Hospital > |
Discharged from the hospital Thursday morning
SREC+Usual product use as regular
Daily Diary
8 Standardized SREC Sessions Free use
8 Standardized SREC Sessions Free use
24-hr BP/HR monitoring
1 blood draw
24-hr urine collection
8 Standardized SREC Sessions Free use
Circadian blood collection
24-hr urine collection

Study locations: The Screening and Orientation Visits will take place at the UCSF Tobacco Research Center (3130 20th Street, Suite 308) and the Inpatient Study Days will take place at the CTSI-CRS (5B Research Ward) at Zuckerberg San Francisco General Hospital (1001 Potrero Avenue, 5th floor).

How long will I be in the study?

Participation in the study will consist of a screening visit (1-2 hours), Orientation visit (1-2 hours), 12 outpatient days, 9 inpatient days for a total of 23 days.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the Clinical Research Coordinator, your CTSI-CRS nurse, or the Study Physician or Nurse Practitioner if you are thinking about stopping or decided to stop.

The Clinical Research Coordinator, Study Nurse Practitioner or Study Physician may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. If you develop side effects, your participation in the study may be stopped, depending upon the severity.

You should talk to the Clinical Research Coordinator, the Study Nurse Practitioner or the Study Physician about any side-effects you experience while taking part in the study.

Risks and side effects related to the study procedures include:

- Venipuncture and Catheterization: A catheter (small plastic tube) will be placed in a vein in one forearm in order to make it easier to take the multiple blood samples. The
catheter will remain in place for about 10 hours. There is a small risk of pain, swelling, bruising, or infection.

- **Blood Loss**: You will lose a total of about 1 cup of blood during the entire study. This amount of blood loss poses no risk to healthy individuals.
- **The Study Procedures** may be inconvenient and tedious (filling out forms, spending time in the hospital, providing specimens, etc.) and you may have trouble staying awake as required.
- **During abstinence**, you may feel may feel withdrawal symptoms from smoking/nicotine withdrawal. The symptoms can be uncomfortable but are typically of minimal risk. These symptoms can include anger, irritability, frustration, anxiety, nervousness, depressed mood/sadness, craving for a cigarette, difficulty concentrating, increased appetite or hunger, weight gain, sleep problems, restlessness, difficulty concentrating, impatience, constipation, dizziness, coughing, dreaming or nightmares, headaches, nausea, and sore throat.
- You may also feel uncomfortable when getting your blood pressure taken depending on the tightness of the cuff.

### Are there benefits to taking part in the study?

There will be no direct benefit to you from participating in this study. However, you may benefit from the knowledge that you are contributing in a very important way to further scientific knowledge concerning harm reduction and health risks for tobacco and e-cigarette users.

### What other choices do I have if I do not take part in this study?

You are free to choose not to participate in the study. If you decide not to take part in this study, there will be no penalty to you.

### Will information about me be kept private?

We will do our best to make sure that the personal information gathered for this study is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include: Representatives of the University of California, the Study Sponsor (National Institutes of Health), and the Food and Drug Administration (FDA).

Participation in research may involve a loss of privacy. But information about you will be handled as confidentially as possible. Two kinds of “charts” are created when you take part in one of our studies:

1. A medical record at the Zuckerberg San Francisco General Hospital will be created because of your participation in this study. Your consent form, hospital nursing forms, and some of your hospital laboratory test results will be included in this record. Therefore, other health care providers may see your test results and become aware of
your participation. Hospital regulations require that all health care providers treat information in medical records confidentially. The forms you fill out during your screening visit, many of the forms filled out during the study, the generic testing results, and the results of assays on the biological specimens collected on the study will **not** become part of your hospital records.

2. We make a “research chart” specifically to hold the forms and sample testing results that do not appear in the ZSFG medical record. You will be given a unique study identification number that will be used in this research chart and on your study samples. This number is different from your medical record number. While the study is in process, we keep some identifying information in this chart so that we are able to contact you, process payments, etc. Once the study is completed, identifying information is removed from the chart and stored separately where it is only available to research personnel who need access to it. Charts and samples are always kept in locked rooms. We keep the link between your identity and your study number and your samples for several reasons. We may want to contact you (with your agreement) to see if you want to participate in additional studies. We also need to keep track of when a subject participates in more than one study so that certain tests are not repeated. Or you may want to contact us later on to ask that your samples be destroyed, and we cannot do this unless we know the link to your research study number.

**Will any research-related procedures be billed to me?**

No. The sponsor has agreed to pay for all procedures associated with this research study; you or your insurer will not be billed.

**Will I be paid for taking part in this study?**

In return for your time and effort, you could be compensated up to a total of $2,500 if all parts of the study are completed. This includes the following:

- **Screening Visit:** $20
- **Study Block Week #1 (4 days Outpatient, 3 days inpatient):** $630  
  - Abstaining the night before hospital admission: $30
- **Study Block Week #2 (4 days Outpatient, 3 days inpatient):** $630  
  - Abstaining the night before hospital admission: $30
- **Study Block Week #3 (4 days Outpatient, 3 days inpatient):** $630  
  - Abstaining the night before hospital admission: $30
- **Bonus for Completion of Study:** $300

You will be compensated $20 for today’s Screening Visit as long as your drug test is negative (marijuana is okay) and the saliva lab results indicate that you are a regular user of the tobacco and/or the e-cigarette products you reported.

You will be compensated $30 for abstaining before each hospital admission if your expired carbon monoxide is below 8 ppm and if you also haven’t used any tobacco and/or e-cigarette products, indicating overnight abstinence from 10pm to 7am hospital admission.
A check will be mailed to you after completion of each portion of the study and it may take up to 4-5 weeks for you to receive your check. You will need to provide your home address and social security number to receive payment.

If your payment checks are not received by the end of 5 weeks from the last day of your study visit for that portion of the study, please contact Ms. Patricia Winston at 415-206-8326.

What happens if I am injured because I took part in this study?

It is important that you tell the study personnel if you become sick or injured. You may directly tell your Study Physician, Delta Dempsey, MD (at 415-641-1465), or the Principal Investigator (Neal Benowitz, MD (at 415-206-8324) if you feel that you have been injured because of taking part in this study.

**Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the call the Office of the Institutional Review Board, at 415-476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to the Clinical Research Coordinator (Jennifer Ko, 415-641-4788), the Project Manager (Natalie Nardone, PhD at 415-514-1450), the Study Physician (Delta Dempsey, MD at 415-641-1465), or the Principal Investigator (Neal Benowitz, MD at 415-206-8324) about questions or concerns you have about this study.

For questions about your rights while taking part in this study, you may call the Office of the Institutional Review Board (a group of people who review the research to protect your rights) at 415-476-1814.
A description of this clinical trial will be available on [http://ClinicalTrials.gov](http://ClinicalTrials.gov) as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

**Future Studies:** The researchers in the Division of Clinical Pharmacology and Experimental Therapeutics at UCSF would like to know if you are interested in participating in future studies for which you may be eligible. By initialing this section of the form, you are giving them permission to keep a file of your information (name, contact information, date of birth, laboratory results, and completed questionnaires) and to re-contact you. You will be under no obligation to actually participate in any new study, and whether or not you initial this section will have no effect on your participation in the current study. You may withdraw permission to be re-contacted at any time by calling the research coordinator or emailing research staff at tobaccocoord@ucsf.edu.

I agree to allow the researchers in the Division of Clinical Pharmacology and Experimental Therapeutics at UCSF to keep my information on file as described above so that I may be re-contacted for possible participation in future nicotine and smoking related studies for which I may be eligible.

CONSENT

You have been given a copy of this consent form and the Experimental Subject’s Bill of Rights to keep.

**PARTICIPATION IN RESEARCH IS VOLUNTARY.** You have the right to decline to participate or to withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled. If you are a student or employee of the University, refusal or withdrawal will not affect your grades or employment status. You may be withdrawn from the study without your consent if the researchers believe that it is in your best interest or if you fail to follow study procedures (for instance, failure to keep appointments or to provide specimens).

If you wish to participate in this study, you should sign below. In addition, you will be asked to sign a separate form authorizing access, use, creation or disclosure of health information from you.

<table>
<thead>
<tr>
<th>Date</th>
<th>Participant's Signature for Consent</th>
<th>Print</th>
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<table>
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<tr>
<th>Date</th>
<th>Person Obtaining Consent</th>
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11.2 SREC PARTICIPANT HANDOUT

NIDA Standardized Research Electronic Cigarette (SREC)

The Standardized Research E-Cigarette, or SREC, was developed by NIDA, or the National Institute of Drug Abuse (part of the NIH), to help researchers assess uncertainties in electronic nicotine delivery devices. This handout describes the characteristics of the SREC device.

Physical characteristics:

![Image of SREC device]

- **Tank:**
  - Sealed and disposable
  - Minimum 350 puffs per tank
  - Volume of e-liquid per tank ~ 3ml

- **Features:**
  - Device unlock/lock mechanism: 5 button presses
  - LED flash confirms lock/unlock

- **Rechargeable Battery:**
  - >400 puffs per charge
  - Battery life-time (≥80% initial capacity): 300 charge cycles
  - Time to full charge: ~90 minutes
  - Output voltage: 3.30 ± 0.05 V
  - Battery storage capacity: 1000 mAh

https://www.drugabuse.gov/funding/supplemental-information-nida-e-cig
E-Liquid Characteristics:

- Tobacco flavored
- Nicotine concentration: 15 mg/ml
- Propylene Glycol ~ 50% (wt / wt)
- Glycerin: ~ 50% (wt / wt)
- Cotinine: <1 µg/g
- Nornicotine: <5 µg/g
- Myosmine: 3 µg/g
- Anabasine: <1 µg/g
- Anatabine: <1 µg/g
- Beta nicotyrine: <1 µg/g
- Diacetyl: <2 µg/g
- 2,3-Pentanedione: <1 µg/g
- Arsenic: <0.1 µg/g
- Cadmium: <0.1 µg/g
- Chromium: <0.1 µg/g
- Lead: <0.1 µg/g
- Nickel: <0.1 µg/g
- Mercury: <0.05 µg/g

Aerosol Characteristics (roughly per puff):

- Propylene Glycol: 3.5 mg
- Glycerin: 3.8 mg
- Nicotine: 100 µg
- Formaldehyde: 0.1 µg
- Acetaldehyde: < 0.1 µg
- Acrolein: < 0.1 µg

https://www.drugabuse.gov/funding/supplemental-information-hiode-cig
11.3 SAMPLE CASE REPORT FORM (CRF)

Date of Screening Visit: ____________ (MM/DD/YYYY)

1. Weight: _________ kg  (Weigh without shoes, coats or heavy sweaters.)
2. Height: _________ cm  (Measure Height without shoes.)
3. BMI = _______  (See EDC for Automatic calculation)
4. Ask subject: “Have you ever fainted or passed out?”  □ Yes  □ No
   If yes, please explain:

Time of Collection of Samples: ____________ (military time)

Automatic BP reading:
5a. BP = _______ / _______
6a. Heart Rate = ________
7. Expired CO = _________ ppm
8. # of Cigs smoked today = __________
9. Time of last Cig smoked = __________ (military time)

Manual BP reading:
5b. BP = _______ / _______
6b. Heart Rate = ________

10. Pregnancy  □ Positive  □ Negative  □ N/A (if male)

11. Urine Toxicology Test:
   □ Positive
   □ Negative
   If positive, name the drug(s):
   □ Marijuana  □ Methamphetamine  □ Barbiturates
   □ Cocaine  □ Opiates  □ Methadone
   □ Amphetamines  □ Benzodiazepines  □ Pcp

Lab Measurements:
12. Saliva Cotinine = __________ ng/mL

13. Nic Alert (if applicable) = ______________  □ N/A
11.4 PRODUCT PACKAGING AND LABELING

Numbered to track the devices and for product weight (before and after use)

Labelled with participant study ID

Study ID: XXXX-XXX