University of California
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Clinical Pharmacology of Electronic Cigarettes

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Manual of Procedures (MOP)

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Table of Contents

1 Table of Contents

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BACKGROUND, GENERAL AIMS & STUDY DESIGN

Electronic cigarettes (EC) are nicotine delivery devices that generate a nicotine-containing aerosol which is inhaled by the user. EC are perceived by users to be useful in helping quitting smoking of conventional tobacco cigarettes (TC) as well as having a presumed lower risk of adverse health effects compared to TC, the potential for use in public places, reduced cost, and lack of the noxious clinging odors associated with TC use. The use of EC has dramatically grown in recent years and is currently estimated to be a billion dollar industry, with over 400 existing brands of EC and the three major U.S. tobacco companies now marketing their own brands. The FDA has announced the intention to regulate EC.

Key questions relevant to FDA regulation include the addictiveness and safety of EC. Many believe that electronic cigarette (EC) function as nicotine delivery devices in the same way as tobacco cigarettes (TC), and that EC will prove to be just as addictive as TC, but this may not be the case because of fundamental differences in the design and method of use of these products. For example, we hypothesize that systemic nicotine exposure will be lower with EC compared to TC; that despite lower nicotine intake EC users will experience similar reward and no greater withdrawal symptoms or craving compared to TC; and that dual EC/ TC users will not titrate their daily intake of nicotine in the same way that TC smokers of high- vs low-yield nicotine TC do.

Our proposal specifically focuses on the areas that are thought to most closely relate to the addictive potential of EC, namely: (1) EC as nicotine delivery devices, covering issues of nicotine intake and pharmacokinetics, temporal patterns of use and titration of nicotine; and (2) subjective effects of EC use, including relationship of use to reward, withdrawal and craving. We will also examine aspects of safety of EC use (by assessment of cardiovascular and hormonal effects of use and of biomarkers of exposure to potentially toxic constituents) and explore the identification and validation of biomarkers that may be useful in distinguishing EC from TC use. Study participants will be dual users of TC and EC so that we may compare both modalities of use in experienced users in a within-participant design.

The study will consist of two 1-week blocks (EC-only or TC-only conditions) with 4 days of outpatient ad libitum product use followed by 3 days in a clinical research ward to include a single-use pharmacokinetic study, monitoring of product use, subjective assessments, blood and urine collections to assess biomarkers, and a 24-hour period of cardiovascular monitoring. Two additional days at the end of the 2nd block will assess similar measurements during a period of nicotine-product abstention.

2 INTRODUCTION AND STUDY DESIGN

2.1 RESEARCH QUESTION

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

2.2 SPECIFIC AIMS

2.2.1 Specific Aim #1

To characterize nicotine delivery, systemic exposure and effects from Electronic Cigarettes.

In dual EC/TC users instructed to use only EC or TC for a week at a time, we will address the following questions:

- What fraction of nicotine inhaled from EC is retained in the body, and how is retention influenced by: the type of device; the concentrations of nicotine, propylene glycol and glycerin in the e-liquid; the pH of the liquid; and the battery voltage? How does the time of peak nicotine concentration compare in EC vs TC use?
- How does the amount of nicotine exhaled from EC use (important as a source of secondhand exposure to non-users) relate to the product characteristics?
- What is the systemic exposure to nicotine from daily use of EC, and how is it influenced by the same product characteristics? How does exposure relate to the nicotine concentration of EC emissions as measured by smoking machine assays?
- How does the daily intake of nicotine during ad libitum use compare for EC vs TC, and is there absolute or relative titration of nicotine intake when switching from one to the other? How much of the systemic nicotine dose from EC is absorbed via inhalation into the lungs and oropharynx vs swallowing into the gastrointestinal tract?
- How do satisfaction, reward, craving and withdrawal symptoms compare for EC vs TC use?
- How does the pattern of puffing compare for EC vs TC use? Are there similar patterns of regular vs clustered use within participants?

2.2.2 Specific Aim #2

To perform preliminary assessments of aspects of safety of Electronic Cigarette use.

- What are the levels of exposure of tobacco smoke toxicants (particularly volatile organic compounds - VOCs) for dual use (baseline) vs EC-alone vs TC-alone vs no-product use? What is the relationship between propylene glycol (PG), glycerin and nicotine concentrations in the e-liquid, the EC emissions, and the urine mercapturic acid metabolite products of propylene oxide and acrolein, respectively?

- How do the cardiovascular effects (circadian heart rate, blood pressure and urinary catecholamine excretion) compare for use of EC-alone vs TC-alone vs no-product?

2.2.3 Specific Aim #3

To validate biomarkers useful in distinguishing Electronic Cigarette use from Tobacco Cigarette use.

- What is the sensitivity and specificity of the ratio of nicotelline to nicotine metabolites (cotinine or total nicotine equivalents) in urine when used to distinguish EC vs TC use?

3 STUDY DESIGN

3.1 DESIGN SUMMARY

This study is an observational, crossover study that will evaluate the addictiveness and safety of electronic cigarettes (EC). It will focus on the areas that are thought to most closely relate to the addictive potential of EC, namely: (1) EC as nicotine delivery devices, covering issues of nicotine intake and pharmacokinetics, temporal patterns of use and titration of nicotine; and (2) subjective effects of EC use, including relationship of use to reward, withdrawal and craving.

3.2 MAJOR STATISTICAL VARIABLES

Predictor Variable List: nicotine intake and pharmacokinetics (24 hour plasma nicotine area under the curve (AUC) during ad lib and total nicotine equivalents (TNEs) in 24 hour urine samples), temporal patterns of use (average and variability 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), and titration of nicotine (ratios of 24 hour AUCs or 24 hour TNEs for EC/TC), levels of reward (CES), withdrawal (MNWS) and craving (QSU).

Primary Outcome: concentrations of nicotine, cotinine, multiple nicotine metabolites in urine, the retention of nicotine, amount of nicotine exhaled, average daily nicotine intake, titration of nicotine intake and estimated swallowing vs inhalation of nicotine.

Refer to Page 3 of the Data Safety and Monitoring Plan for secondary and tertiary outcomes.

3.3 PRIMARY RESEARCH SAMPLES

Plasma: nicotine, cotinine, 3-Hydroxicotinine (3HC), IL-6, C-reactive protein, s-ICAM, angiopoietin-2 and vascular endothelial growth factor (VEGF).

Urine: nicotine, nicotine metabolites (nicotine equivalents), NNAL, catecholamines, mercapturic acid biomarkers of acrolein and propylene oxide, and other volatile organic compounds (VOCs), minor alkaloids (including anabasine, anatabine, and nicotelline), 8-iso-PHF alpha, 11-dehydro-TxB2.

A detailed Schedule of Assessments outline number of samples and assays is located in the Crossover Study folder on the t-drive under Databases.

3.4 STUDY TIMELINE

- Application submitted to the Institutional Review Board (IRB): 3/19/2015
- Approval date: 3/23/2015
- Expiration date: 3/22/2018
- Dates of enrollment: 12/7/2015-2/2/2018

3.5 ELIGIBILITY

Potential participants will express interest in participation by calling the UCSF Tobacco Research Center Recruitment Line, filling out the secure REDCap survey hyperlink from the Craigslist ad, or by emailing the UCSF Tobacco Research Center email address. Participants will be contacted to take part in a confidential phone screen or 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.

3.5.1 Inclusion Criteria

- Healthy on the basis of medical history and limited physical examination.
  - 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
  - Using same EC device at least 15 days out of the past 30 days
  - Nicotine strength of e-liquid ≥ 6 mg/mL, if using a 2nd or 3rd generation device, or willing to use a 6mg/mL strength e-liquid for the duration of the study
  - Conventional TC (≥ 5 CPD for past 30 days)
  - Carbon monoxide ≥ 5 ppm or per discretion of Principal Investigator
  - Saliva cotinine ≥ 50 ng/mL or urine cotinine via NicAlert
- EC device is one of the most popular 1st, 2nd, or 3rd generation brands (with the exception of rebuildable atomizers) as determined at time of study commencement
- Age: ≥ 21 years old

3.5.2 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
  - Use of medications that are inducers of nicotine metabolizing enzyme CYP2A6 (Example: rifampicin, dexamethasone, phenobarbital, and other anticonvulsant drugs)
  - 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.
- Planning to quit smoking within the next 60 days

3.5.3 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 Principle 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.

3.5.4 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.

3.54a 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.

3.54b 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.

4 IDs & Assignment

4.1.1 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 "6885" to refer to the CTSI-5B study number, which is how the study is referred to at the research ward. These numbers will be followed sequentially starting from 001. For example, the first participant enrolled will have a Study ID of 6885-001.

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.

4.1.2 Assignment Procedure

The participant will be assigned to one of two groups:

1) Electronic Cigarette (EC) 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 both tobacco and e-cigarette products in case the assignment changes. The final product assignment will take place at the orientation visit. The CRC will refer to the "6885 Eligible Participants 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.

Study group assignment will be based on the following Assignment Schedule:

(NOTE: Participant ID in the table below may or may not correspond to Participant Study ID)

E-Cigarette Crossover Assignment Schedule

	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC
	Participant 7	Participant 8	Participant 9	Participant 10	Participant 11	Participant 12
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC
	Participant 13	Participant 14	Participant 15	Participant 16	Participant 17	Participant 18
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC
	Participant 19	Participant 20	Participant 21	Participant 22	Participant 23	Participant 24
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC
	Participant 25	Participant 26	Participant 27	Participant 28	Participant 29	Participant 30
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC
	Participant 31	Participant 32	Participant 33	Participant 34	Participant 35	Participant 36
Block #1	TC	EC	TC	EC	TC	EC
Block #2	EC	TC	EC	TC	EC	TC

5 PARTICIPANT WITHDRAWAL

5.1.1 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.

5.1.2 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 as follows:

- Inpatient admission Study Block #1

- Day 1 - $200
- Day 2 - $400
- Day 3 - $600

If the participant does not complete the early morning procedures on the morning of Day 4 before discharge, he/she will still be compensated $600 for completion of the full study block

- Inpatient admission Study Block #2:
  (amounts would also include + $600 for completion of Study Block #1)
  - Day 1 - $180
  - Day 2 - $360
  - Day 3 - $540
  - Day 4 - $720
  - Day 5 – N/A, participant would get full $900 +$500 bonus

"Day" indicates a full 24 hours of procedures. If the participant leaves in less than 24 hours of that day, the CRC and Project Manager will discuss providing compensation for a partial amount.

5.1.3 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.

5.13a Contact Attempts

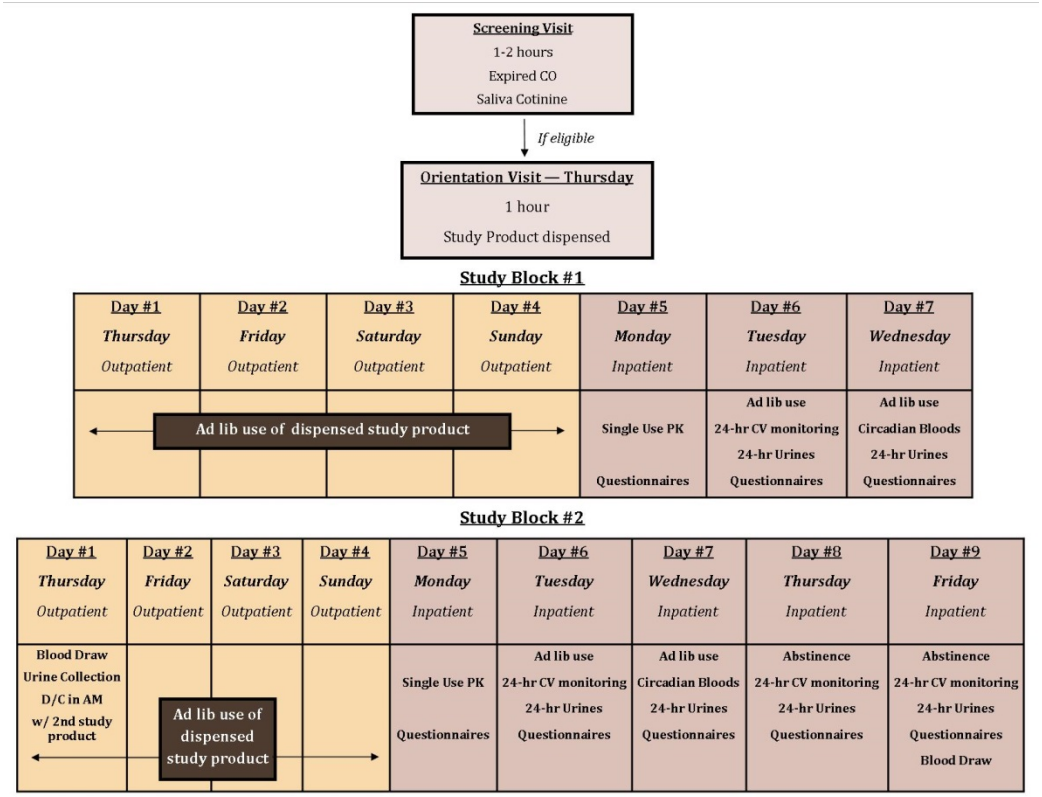
After three unsuccessful phone and email contact attempts, a letter of intent to contact will be mailed to the participant's home address. This letter will inform the participant that they will be formally withdrawn from the study by the date that is 90 days past the last point of contact. It will also 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.

5.13b 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 3.5.4 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.

6 VISIT SCHEDULE

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



6.1.1 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 1

Assessment Point	Maximum Time allowed from Phone/Email Screen	Maximum Time allowed from Screening Visit

Phone/Email Screen		
Screening Visit	30 days	
Orientation	120 days	90 days

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 3.5.4.

6.1.2 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.

7 RECRUITMENT METHODS

Our methods of recruitment will be as follows:

- Postings to craigslist (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
- 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 by phone or email 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.

7.1 PRELIMINARY REDCAP SCREENING

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

The preliminary REDCap screen ("UCSF Tobacco Research Email 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, and schedule these participants to come in for an in-person screening visit.

7.2 CONFIDENTIAL PHONE SCREEN

At the beginning of this study, a Confidential Phone Screen was used before migrating exclusively to the REDCap Screening. The CRC will call eligible individuals, as described above, to conduct a thorough Confidential Phone Screen. Additionally, individuals who call the UCSF Tobacco Research Center Recruitment Line directly will undergo the phone screen. Data generated from this phone screen will be entered into REDCap. The CRC will explain that questions will be asked regarding the individual's tobacco product use and health history, and that the expected length of the screen is approximately 10 minutes.

Procedures for the Confidential Phone Screen include the following:

- The CRC will record the participant's personal information in a secure Access Database. This includes their name, phone number, email address, date of birth, and address.
- After completing the Access Database fields, the CRC will open REDCap and start a new entry. The REDCap ID number that populates will be copied into the Access Database to connect the personal information to the screening data. No identifiers are recorded in REDCap.
- The CRC will administer a series of eligibility questions, collected in the Phone Screen REDCap form ("E-Cigarette R01 & Flavors Study Screen").
- The CRC will determine if the participant is eligible to attend an in-person screening visit based on the inclusion/exclusion criteria.

If the participant is ineligible during the phone screen, the CRC may choose to end the phone screen when appropriate. In the event of an eligible participant, an in-person screening will be scheduled immediately.

7.3 EMAIL SCREENING PROCEDURES

Individuals who email the UCSF Tobacco Coordinator email address 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 ("Crossover Study Email Screen"). The REDCap Email Screening Survey has all of the same questions as the Confidential Phone Screen, but is in a survey format that the participants will fill 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 call the participant to schedule them to come in for an in-person screening.

8 STUDY VISITS AND PROCEDURES

8.1 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, a MILCOM, 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:

8.1.1 Consent

Upon initiation of the screening visit, the CRC will greet the participant and ask to see a valid form of identification to verify their age. Next, the CRC will 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. Two 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. Additionally, the participant will be asked to review and sign two HIPAA forms, and a third copy will be given to the participant for their records. The participant will also be asked to read a copy of the Bill of Rights to ensure that the participant is aware of his/her rights in participating in a research study.

8.1.2 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."

8.1.3 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.

8.1.4 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, CRC may proceed with screening visit and the PI will use their discretion to determine eligibility.

8.1.5 Screening Packet

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

- **Section 1: Personal Data Form**
  - This section contains the participant's contact information as well as an Emergency Contact.
- **Section 2: Demographics**
  - This section contains information regarding the participant's gender, age, ethnicity, race, and education.
- **Section 3: Tobacco Product Use**
  - 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**

- 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 4 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.

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

8.1.6 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."

8.1.7 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.

8.1.8 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 will not be entered into an electronic database. The CRC will complete the Screening Visit Log (#6885 Participant Log & Tallies) and enter data from the Screening Packet into the "Crossover 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.

9 PREPARATION FOR INPATIENT PORTION

9.1.1 Product Purchasing

The CRC will purchase the participant's EC or TC products from local vape or 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. In order to determine total EC products, the CRC will refer to Screening Packet, Section 3: E-Cigarette History, questions #4 and #6 in order to get a proper approximation of how much e-liquid the participant uses per day. Refer to Section 9.2.2. for description of the calculations.

9.1.2 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:

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.

Consent Form and HIPAA

- An original signed copy of the consent form and HIPAA from the Screening Visit will be included in the set-up.

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 and EC product brands.

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.

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.

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.

Other Study Forms

- Caffeine Log is included to track participants' inpatient caffeine intake
- Study Questionnaires included are the following: Questionnaire of Smoking Urges (QSU), modified for E-Cigarettes Cigarette Evaluation Scale (mCES), Positive and Negative Affect Scale (PANAS), and Minnesota Behavioral Scale (MNWS)
- The Outpatient Withdrawal Form is used to describe symptoms that participants felt over the outpatient study period (Thursday-Sunday). The Withdrawal Form asks participants to rate their symptoms on a scale of 1-5. For participants who rated any given withdrawal symptom as being a 3 or 4, the CRC followed up with the participant to ask which outpatient days they had those symptoms, and if any day was more intense than any other. These notes were recorded next to the corresponding item on the form.
- The 48-Hour Product Use Form was intended to be used to track outpatient product use in cases where participants did not fill out their product diaries over the outpatient period. This form was kept on hand, but never used for any of the participants.
- The End of Study Questionnaire was given to participants on the final day of the study in the second block, and asked about their compliance with study procedures during the study.

9.2 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:

9.2.1 Product Assignment

The CRC will input the participant's initials, product assignment, and date he/she is assigned to that condition into the "6885 Eligible Participants Log". Product assignment procedures are described in Section 4.1.2.

9.2.2 Distribution of Study Products

Participants will be given EC 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.

For the 1st generation EC users, the EC device as well as the cartridges (if applicable) will be provided in the participant's preferred flavor. For 2nd generation, we will only provide the e-liquid vials. In the case of multiple e-liquid vials or cartridges, each vial/cartridge will be numbered with a label or via a sharpie pen before weighing.

The amount of devices or cartridges to provide will be estimated using the participant's self- reported daily product usage on their screening packet. Light to medium users will be given 1 vial or 3 cartridges to use over the outpatient period, and 1 vial or 3 cartridges will be purchased for their use during the inpatient period. Heavier users will be given 2 vials or 5 cartridges to use over the outpatient period, and 2 vials or 5 cartridges will be purchased for their use during the inpatient period. Before distributing any of the devices/cartridges or e-liquid vials, they will be labeled with a sharpie and this weight will be recorded on the center of the Product under "Ad Lib Use". The weight of that distributed e-liquid or cartridge after the participant's use upon collection the following day can be found below the Ad Lib Use section under "Returned Products".

For the TC products, the number of cigarette packs provided will be determined by the participant's self-reported cigarettes per day on their Screening Packet, plus additional cigarettes to account for their exclusive use of one product. The amount to purchase for both outpatient and inpatient will be calculated as: (cigarettes per day *7) + 1 pack, rounded to nearest pack. The participants will be asked to collect their cigarette butts during their outpatient and inpatient study

days. These butts will be collected and weighed. The weights for the cigarette butts can be found on the TC Product Weights form.

Participants will sign a product accountability form and be instructed to return all empty and unused products at the end of their outpatient period.

9.2.3 Product Use Diary

Participants will be asked to keep track of their product use during their outpatient days. Instructions for using the TimeJot app or paper diary will be reviewed at the Orientation Visit.

As the TimeJot app is not compatible with an Android phone, participants who own an Android will use a paper diary. On the paper diary, they will record their smoking start and end time, and how many puffs they take. At the end of each outpatient day, the participant will take a picture of the paper diary and email it to the CRC.

For the TimeJot app, participants will be instructed to select a pre-programmed button on the TimeJot app that records the participants' smoking/vaping sessions. Participants will select the "Start" button when they begin a smoking/vaping session and a "Stop" button when they end. The information recorded in the TimeJot app is the date and duration of the sessions in seconds. 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.

9.2.4 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."

9.3 STUDY BLOCK #1

9.3.1 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 the TimeJot app or paper diary, recording every time they start/stop a TC or EC session. After they have completed their use for the day, they will email the summary report to the CRC. If participants have not emailed their summaries by the following morning, the CRC will send them a reminder email.

9.3.2 Admission & Inpatient Days

After the 4 outpatient days, participants will check into the 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**, the following will occur:

- A plastic catheter (thin flexible tube) will be inserted into a vein on the participant's forearms (this will be used to withdraw multiple blood samples and will be kept in place for about 10 hours). The participant will be given a light breakfast and, if he/she normally drinks caffeinated beverages, he/she will be allowed a cup of his/her usual beverage (coffee or tea).
- Between 8:50-9:00am (depending on the assigned study product), the participant will be asked to smoke a commercial cigarette or e-cigarette device and to take puffs only at times signaled by the voice recorder or research team.
    - If this is an e-cigarette device the puffs will be directed as follows: **taking one puff every 30 seconds for a total of 15 puffs on 1st generation devices and 10 puffs on 2nd/3rd generation devices.**
    - If this is a tobacco cigarette, puffs will be directed as follows: **taking one puff every 30 seconds until cigarette is consumed.**
- After each puff, we will capture the smoke the participant breathes out by asking him/her 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 smoke into the traps. There will be NO contact between the participant's 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 cigarette during the standardized session.
- The participant will not be allowed to smoke again until 4 hours later, at which time he/she will be given his/her usual TC or EC and allowed to smoke it as he/she wishes.
- Blood samples, about one teaspoon each, will be withdrawn just before smoking, and after the standardized session. Then during the 4-hour abstinence period, blood draws will take place at 2, 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes.

- The participant will also be asked to fill out several *Questionnaires* about his/her smoking experience before and after smoking the TC/EC and during the 4 hours when he/she is not smoking.
- The participant will not be allowed to doze or sleep during the day. The CRC or nurse may wake the participant if they appear to be sleeping.

On **Day #6**, the following will occur:

- The participant will be allowed to smoke his/her cigarettes or electronic cigarette device as desired from 8am to 12am midnight.
- The time of each cigarette or EC puff will be recorded using the TimeJot smartphone app or paper diary and all cigarette butts and EC 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 also be asked to fill out several *Questionnaires*.
- There will also be 24-hour *urine collections*.

On **Day #7**, the following will occur:

- On the morning of Day #3, an intravenous catheter (like on Day #1) will be placed for blood collections every four hours from 8am to midnight, and at approximately 8am the next day.
- The participant will also be asked to fill out several *Questionnaires*.
- There will also be 24-hour *urine collections*.
- The participant will be discharged the following morning (Study Block #2, Day #1) after his/her last blood draw and urine collection.

9.4 STUDY BLOCK #2

9.4.1 Outpatient Days

After being discharged from the research ward, participants will be able to use their electronic cigarette device or tobacco cigarette product as they wish for another 4 outpatient days. Just as in the outpatient days for Study Block #1, they will use track their product use with a smartphone diary app or paper diary.

During this outpatient period, the CRC will closely monitor participants' entries in the TimeJot app or paper diary, as described in Section 9.2.3.

9.4.2 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 admitted for a period of 5 days using the alternate product.

The first 3 days of the admission will follow the same procedures as the first admission, with an additional two day abstinence period in which the participant will be asked not to use any products. During the abstinence period, there will be 24-hour *urine collections*, 24-hour *cardiovascular monitoring*, and *Questionnaires*.

On **Day #8**, the following will occur:

- The participant will abstain from all product use.
- The participant will fill out several *Questionnaires*.
- 8-hour *urine collection* from 8am-4pm followed by a 24-hour *urine collection* beginning at 4pm.
- 24-hour *ambulatory blood pressure and heart rate* will begin at 8am.

On **Day #9**, the following will occur:

- The participant will continue with 24-hour ambulatory blood pressure and heart rate recorder for *cardiovascular monitoring* until 4pm.
- The participant will also be asked to fill out several *Questionnaires*.
- There will continue to be 24-hour *urine collections* until 4pm.

9.5 Summary of Standardized Puffing Protocols

- Electronic Cigarette ARM 1st Generation Device:
  1 puff every 30 seconds for a total of 15 puffs

- Electronic Cigarette ARM 2nd/3rd Generation Devices:
  1 puff every 30 seconds for a total of 10 puffs

- Tobacco Cigarette ARM:
  1 puff every 30 seconds until the cigarette is completely smoked

9.6 Product Weighing Procedures

For the EC 1st Generation Devices, our weighing procedure was the following:

- Pre-Outpatient Period – The CRC would label each 1st generation device with a sequence number using a sharpie. CRC would weigh each device without any product packaging.
- Pre-standardized session – The device and/or cartridges were weighed by the CRC prior to the standardized session and recorded on the EC Product Weights Form to account for the outpatient product usage. After this, GSH weighed the entire device (including the cartridge) prior to the standardized session and recorded this weight on the PK Product Weights Form. This information was copied to the EC Product Weights form by the CRC, and can be found under the "Standardized Session" portion of the form.
- Post-standardized session – GSH weighed the entire device (including cartridge) after to the standardized session and recorded this weight on the PK Product Weights Form. This information was copied to the EC Product Weights form by the CRC, and can be found under the "Standardized Session" portion of the form.
- Pre-distribution each inpatient study day – After the standardized session, the device and/or cartridge used in the standardized session was weighed again to use as a baseline for ad-lib use later in the day that did not included use during the standardized session. While GSH always weighed the entire device for the standardized session, all other weights recorded during the inpatient and outpatient period were done as following: for disposable devices, the entire device was weighed, and for devices with cartridges, only the cartridge was weighed. This weight was recorded on the EC Product Weights Form.
- Post-use each inpatient study day – Each study day, the nurses went into the participant's room at midnight to collect their products. The following morning, the CRC weighed the device and/or cartridge on the scale in the clean utility room, and recorded this weight on the EC Product Weights Form.

For the EC 2nd or 3rd Generation

- Pre-Outpatient Period – The CRC would label each e-liquid vial with a sequence number using a sharpie. CRC would weigh each e-liquid vial (without the cap).
- Pre-standardized session – The e-liquid vials that the participant used during the outpatient period were weighed (cap removed) by the CRC prior to the standardized session, and recorded on the EC Product Weights Form to account for the outpatient product usage. For e-liquid vials that utilized a dropper, the residual e-liquid contained in the dropper was squeezed into the vial prior to weighing. After this, GSH used some of the e-liquid to fill the device. Then, he weighed the entire device prior to the standardized session and recorded this weight on the PK Product Weights Form. This information was copied to the EC Product Weights form by the CRC, and can be found under the "Standardized Session" portion of the form
- Post-standardized session – GSH weighed the entire device after to the standardized session and recorded this weight on the PK Product Weights Form. This information was copied to the EC Product Weights form by the CRC, and can be found under the "Standardized Session" portion of the form.
- Pre-distribution each inpatient study day – On PK days, the e-liquid vial used in the standardized session was weighed again to use as a baseline for ad-lib use later in the day that did not included use during the standardized session. While GSH always weighed the entire device for the standardized session, all other weights recorded during the inpatient and outpatient period were for the e-liquid vial only. For e-liquid vials that utilize a dropper, the residual e-liquid contained in the dropper was squeezed into the vial prior to weighing. This weight was recorded on the EC Product Weights Form.
- Post-use each inpatient study day – Each study day, the nurses went into the participant's room at midnight to collect their products. The following morning, the CRC weighed the e-liquid vial on the scale in the clean utility room, and recorded this weight on the EC Product Weights Form to account for the participant's product usage the previous day. For e-liquid

vials that utilize a dropper, the residual e-liquid contained in the dropper was squeezed into the vial prior to weighing.

For the tobacco cigarettes, our weighing procedure was the following:

- Pre-Outpatient Period – The CRC would weigh 1 sample tobacco cigarette from a pack and record as pre weight on the "Average cigarette weight" on the TC Products outpatient period.
- Post-Outpatient Period – The participant collected cigarette butts and the CRC counted all butts and all remaining packs/cigarettes that were brought back. The CRC calculated the amount of tobacco burned as: "=(average cigarette weight * number of cigarettes smoked)-(average weight * number of cigarettes smoked). If there was a discrepancy from what the participant smoked and amount of cigarette they returned, the CRC evaluated the number of cigarette smoked and used that in the calculation above.
- Note: the "Average cigarette weight" recorded on the TC Product Weights form for the outpatient period may differ in weight slightly from the "Average cigarette weight" on the TC Product Weights form during the inpatient period. This is because when a cigarette is weighed prior to distribution at Orientation, it is weighed on the scale at the Tobacco Research Center. On the first day of the inpatient period (PK day), the cigarette is weighed on the scale in the Clean Utility Room of the hospital. This weight is used for the rest of the inpatient period.
- Pre-standardized session – A cigarette from the participant's pack was weighed by the CRC in the clean utility room prior to the standardized session, and recorded on the PK Product Weights Form and TC Product Weights Form.
- Post-standardized session – After the standardized session, the CRC weighed the cigarette butt in the clean utility room and recorded this weight on the PK Product Weights Form and TC Product Weights Form.
- Pre-distribution each inpatient study day –The weight of one cigarette from the participant's pack was weighed in the clean utility room on the first inpatient study day, and recorded under the "Average cigarette weight" portion of the TC Product Weights form. The weight of this cigarette was used as the average cigarette weight for all other inpatient

study days. Each day, the number of cigarettes distributed was recorded on the TC Product Weights Form.

- Post-use each inpatient study day – Each study day, the nurses went into the participant's room at midnight to collect their products. The following morning, the CRC weighed the returned cigarette butts in the clean utility room and recorded this weight on the TC Product Weights Form to account for the participant's product usage the previous day. Under returned products, the "Total Weight" is equal to average cigarette weight * number of cigarette butts. "Average Weight" is equal to Total Weight/number of cigarette butts. "Tobacco Burned"=(average cigarette weight * number of cigarettes smoked)-(total weight). In cases where the participant was missing a butt or returned an extra butt, the "Tobacco Burned" was calculated as: "=(average cigarette weight * number of cigarettes smoked)-(average weight * number of cigarettes smoked).

9.7 PARTICIPANT COMPENSATION

Participants will be compensated according to Table 2:

Table 2

	Screening Visit	Study Block #1	Study Block #2	Completion Bonus
Compensation	$30*	$600	$900	$500
Total Compensation				**$2,030**

*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 5.1.2.

10 ADVERSE EVENTS AND PROTOCOL DEVIATIONS

10.1 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.

10.2 REPORTING ADVERSE EVENTS

Reporting of serious adverse events will follow the current requirements of the 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 IRB 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 advents 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 profession 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 IRB. 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.

10.3 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 IRB.

11 DATA COLLECTION AND MANAGEMENT

11.1 DATA COLLECTION FORMS

All of the following measures will be collected.

Screening Process:

- UCSF Tobacco Research Email Screen 5/26/2015-2/23/18
- E-Cigarette R01 & Flavors Study Screen (04/01/2015-05/26/2015)

In-Person Screening Visit:

- MILCOM
- Screening Packet

Inpatient Study Visits:

- Day 5, Block 1 & 2:
  - Outpatient Withdrawal Form
  - 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:
  - 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:
  - 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 8, Block 2:
  - Questionnaire of Smoking Urges (QSU) or modified for E-Cigarettes
  - Positive and Negative Affect Scale (PANAS)
  - Minnesota Behavioral Scale (MNWS)
- Day 9, Block 2:

- Questionnaire of Smoking Urges (QSU) or modified for E-Cigarettes
- Positive and Negative Affect Scale (PANAS)
- Minnesota Behavioral Scale (MNWS)
- End of Study Questionnaire

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

12 DUTIES AND RESPONSIBILITIES OF STAFF

12.1 PRINCIPAL INVESTIGATOR

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

12.2 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.

12.3 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.

12.4 PROJECT MANAGER

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

12.5 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.

APPENDIX A: DATABASE GUIDE

Schedule of Assessments

The Schedule of Assessments is a list detailing the various specimens, forms, and questionnaires that are taken and administered throughout the study on any given study visit/study day. Additionally, this form lists the number of samples taken, the analysis type for each specimen, the sample labels before and after processing, and the number of aliquots post-sample processing.

- Location: t-Drive
- Folder: 6885 Crossover E-Cigarettes
- Sub-folder 1: Databases
- Subfolder 2: Schedule of Assessments
- name "Updated Schedule of Assessments 3.9.18"

Screening Visit

1. Screening Log

The Screening Log is a list of all participants who came into the 20th street Tobacco Research Center for a screening visit for the Crossover study. This log details information about each participant as well as the outcome of the visit. Specifically, the Screening Log contains the following information: participant's name, date of screening visit, RedCap ID from the RedCap pre-screening email survey, study ID number, toxicology and pregnancy screening results, eligibility status and reason, ethnicity, race, sex, 5B status (including whether or not the participant was a no-show)and 5B start and end date.

- Location: t-Drive
- Folder: 6885 Crossover E-Cigarettes
- Sub-folder 1: Databases
- Subfolder 2: Screening
- name "#6685 Participant Log & Tallies"
- Password: 6885enr

2. Saliva Cotinine Screening Log
   The Saliva Screening Log is a list of the cotinine values for participants who came in for a Crossover screening visit.
   - Location: s-Drive
   - Folder: Clinical Research
   - Sub-folder 1: Screening Log
   - Subfolder 2: E-Cigarette Crossover Study
   - name "ECigarette Crossover Saliva Cotinine Screening Log"
3. Eligible Participant's Log (only participants deemed eligible at screening)
   The Eligible Participant's Log is a list of all participants deemed eligible to participate in the Crossover study after their screening visit. This log contains the following information: participant's name, study ID, product assignment number, starting product, MRN number, 5B admission and discharge date, and notes regarding withdrawals, no-shows and early discharges. Overall, we had 54 eligible participants, and 36 completed participants.
   - Location: t-Drive
   - Folder: 6885 Crossover E-Cigarettes
   - Sub-folder: Databases
   - name "#6685 Eligible Participants Log"

4. E-Cigarette Crossover Database
   The data collected at the screening visit is located on RedCap under the project titled E-Cigarette Crossover Database. This project includes the following forms: Participant Summary Form, Screening Eligibility Checklist, Screening Packet, Physiological Assessment, NDSS, CES-D, and Wisconsin Inventory of Smoking Dependence Motives.
   - Location: https://redcap.ucsf.edu/redcap_v8.1.7/index.php?pid=10780
5. Product Photo Database
   The product photos for each participant who came in for a screening visit are located on the Product Photos Database.
   a. Location: t-Drive
   b. Folder: 6885 Crossover E-Cigarettes
   c. Sub-folder: Study Coordinator Files
   d. folder name "Product Photos"

Full Study Participant Data

1. Inpatient Caffeine Log
   The Inpatient Caffeine Log details caffeine intake for participants during their inpatient study days.
   a. Location: t-Drive
   b. Folder: 6885 Crossover E-Cigarettes
   c. Sub-folder: Databases
   d. name "#6685 Participant Caffeine Intake"
2. E-Cigarette Device Summary
   The E-Cigarette Device Summary is a list of the device names, generation and e-liquid constituents that each participant used during the study.
   a. Location: t-Drive
   b. Folder: 6885 Crossover E-Cigarettes
   c. Sub-folder: Databases
   d. name "#6885 Crossover E-Cigarette Devices Summary"
3. Crossover Specimen Log
   The Crossover Specimen Log is a file is a database used to track all of the specimens collected during participants' orientation visit and inpatient study days. This log contains the following information: specimen type, dates and

times of specimen collection, date of lab sample transfers, and volume/pH of urine specimens.

a. Location: t-Drive
b. Folder: Clinical Research Operations
c. Sub-folder 1: Lab Processing and Reference
d. Sub-folder 2: Specimen Logs
e. name "6885 6885 E-Cig XO Specimen Log"

4. Urine Catecholamine Summary

The Urine Catecholamine Summary contains the catecholamine data from each participant, including: creatinine, epinephrine, and dopamine per volume, per 24 hours, and ratio to CRT.

- Location: t-Drive
- Folder: 6885 Crossover E-Cigarettes
- Sub-folder 1: Databases
- Sub-folder 2: Urine Catecholamines
- name"#6885 Urine Catecholamine Summary"
- Information is downloaded from ARUP Labs using the login information below, then saved in the Urine Catecholamine Summary excel file
    i. Website: https://www.aruplab.com/ii/login.jsp
    ii. Username: ucsftobacco
    iii. Password: Tobacco1!

5. Product diaries (for participants who used TimeJot app) (source data)

The product diaries database is where the diaries are saved for participants that used the Time Jot app. All other diary entries can be found as the paper version in the participant's binder, or on RedCap.

a. Location: t-Drive
b. Folder: 6885 Crossover E-Cigarettes
c. Sub-folder 1: Databases
d. Sub-folder 2: Product Diaries

6. Cardiovascular Monitoring (source data)

The Cardiovascular Monitoring database is where the CV data can be found for all participants.

a. Location: t-Drive
b. Folder: 6885 Crossover E-Cigarettes

c. Sub-folder 1: Databases
d. Sub-folder 2: 24 hour Cardiovascular Monitoring

7. E-Cigarette Crossover Database

   The E-Cigarette Crossover Database is a database in RedCap where most study data has been entered. This database includes the following forms: Product Accountability Form, Product Weight Form, product diaries, inpatient participant weights, Pre-Standardized Questionnaire, Post-Standardized Questionnaire, 2-Hour Abstinence Questionnaire, 4-Hour Abstinence Questionnaire, 8am Ad-Lib Questionnaire, 8:15 am Ad-Lib Questionnaire, 12pm Ad-Lib Questionnaire, 4pm Ad-Lib Questionnaire, 8pm Ad-Lib Questionnaire, 8am Abstinence Questionnaire, 12pm Abstinence Questionnaire, 4pm Abstinence Questionnaire, 8pm Abstinence Questionnaire, 24-hour cardiovascular monitoring data, 48-hour Product Use Form, End of Study Questionnaire, Withdrawal Symptoms Questionnaire, and adverse event reports.

   - Location: https://redcap.ucsf.edu/redcap_v8.1.7/index.php?pid=10780

8. 6885 CV Data (cleaned data)

   The 6885 CV Data is a project in RedCap that includes the CV data from all Crossover participants. Individual data points on this project may differ slightly from those on the 24-hour cardiovascular monitoring form on the E-Cigarette Crossover Database. The cardiovascular data on the E-Cigarette Crossover Database was entered into RedCap manually, whereas the data on this project was imported directly into RedCap from the source.

9. 6885 Diary Data (cleaned data)

   The 6885 Diary Data is a project in RedCap that includes the diary data from Crossover participants. Individual data points on this project may differ slightly from those on the product diary form on the E-Cigarette Crossover Database. The product diary data on the E-Cigarette Crossover Database was entered into RedCap manually, whereas some of the data on this project was imported directly into RedCap from the source.

APPENDIX B: STUDY POST-MORTEM

- Eating times on nurses flow sheets. Indicate exactly when it is okay for them to eat, around study procedures.
- Get 6mL of e-liquid for Gideon ahead of time, prior to the PK day for e-cig
- The study procedures need to be changed so that participants do not get the $30 bonus check if they vaped the morning of PK day, rather than just having the CO<5 requirement.
    - $30 gift card that morning if they abstain
    - We will do Expired CO
    - We will do "bogus pipeline" for vaping
    - We will tell them that we are checking for both
- MD orders and nurses flowsheets should specify that single stick blood draws using a butterfly needle are okay at the participant's request. Some participant's preferred this and Delia had to write this in the orders each time.
- Specify the pre-blood draw on the nurses flowsheets as its own discrete step on PK days.
- Have the nurses check on the participant's ABPM every 4 hours or so (put in nurses flowsheets). Instruct the nurses to press the manual button if there are repeated errors.
- Get rid of the note page on each inpatient questionnaire.
    - CRC notes should just be recorded on the session log.
- Get rid of the volume portion on the EC product weights form (unless we start using mathematical formula using starting volume, initial wt. and final wt. to calculate exact volume used).
- In the nurses flowsheet on the mornings when the ABPM will be placed, write in something along the lines of "Do NOT let the participant shower after 7:30 AM).
- Have the nurses place the cuff instead of the CRC, but CRC can do the first reading or we train them to turn on and do it.