Vaping THC: a Novel Evaluation of Intake and Pharmacokinetics

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Manual of Procedures (MOP)

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1 INTRODUCTION AND STUDY DESIGN

1.1 Background

Electronic cigarettes for nicotine delivery

Electronic cigarettes (e-cigarettes) have proliferated at a rapid rate since their introduction into the US market in 2007 and their use as a form of nicotine delivery far outpaced the science base (1, 2). Important questions revolved around their abuse liability and safety. Although the design of these devices continues to evolve, we have previously described nicotine intake, systemic retention, pharmacokinetics, and effects, as well as vaping behavior and self-administration of e-cigarettes (3, 4). We showed that e-cigarettes deliver as much nicotine from 15 puffs as a typical tobacco cigarette (~1 mg), most of which is systemically retained, and the shape of the plasma nicotine concentration-time curve is also similar to tobacco cigarettes, except that the maximum plasma nicotine concentration is, on average, lower for e-cigarettes. During *ad libitum* access, e-cigarettes were vaped intermittently in groups of 2-5 puffs or single puffs such that plasma nicotine levels rose gradually and peaked at the end of the 90-minute session. This differs from the rapid increase in plasma nicotine observed during controlled use of e-cigarettes or during tobacco cigarette smoking. Taken together, these results indicate that e-cigarettes have the potential to produce and sustain nicotine addiction but their use and abuse liability may differ from tobacco cigarette.

Electronic cigarettes are NOT restricted to nicotine

Marijuana is the most widely used illicit drug (5). While marijuana has traditionally been combusted, currently vaping of either loose leaf marijuana or other forms of · -9-tetrahydrocannabinol (THC) oil has been increasing (6). The latest national data show that 7.6% of current marijuana users (past 30 days) and 9.9% of ever marijuana users (lifetime) administered THC through a vaporizer or electronic device (6) (the study did not differentiate between vaporizers and electronic devices like e-cigarettes). The prevalence of vaped marijuana or THC is higher among younger adults. Prevalence of vaped marijuana/THC among 18-24 and 25-34 year-old ever marijuana users was 19.3% and 16.3%, respectively, compared to 8.8% for 35-49 year-olds and 5.7% for those 50 years and over (6). A recent study also showed high rates of cannabis vaping using e-cigarettes among high school students (18.0% among ever e-cigarette users) (7).

Combined effects of tobacco and marijuana.

The combined inhalation of tobacco and marijuana is common. Smoking of marijuana in a cigar wrapping (a blunt) is very popular among adolescents and young adults, particularly in the African American population. Smoking of a combination of tobacco and marijuana in cigarette form is also common, particularly in Europe (8) (9). Since both marijuana and tobacco are consumed by vaping, it is likely that vaping of both products will also soon become common. Very little is known about the pharmacology and safety of simultaneous intake of nicotine and THC from vaping.

1.2 RESEARCH QUESTIONS

To understand THC pharmacology and safety of cannabis vaping, including the pharmacology and safety of co-administration of nicotine and THC.

1.3 SPECFIC AIMS/OBJECTIVES

1. To characterize Δ^9-tetrahydrocannabinol (THC) delivery, systemic exposure, and effects from vaping THC-containing cannabis leaf alone or cigarette tobacco alone, or the combination of cannabis and tobacco.

2. To assess sympathetic nervous system (SNS) stimulating and subjective SNS-related effects of THC alone compared to nicotine (tobacco) alone or combined to THC and nicotine co-administration.

3. To assess emissions of THC, terpenes, and other compounds from electronic THC delivery devices.

1.4 STUDY DESIGN

1.4.1 Design Summary

The study is designed as a within-subjects single-blinded crossover study. Fourteen smokers of tobacco cigarettes and cannabis will switch between three conditions, namely: (a) vaping cannabis leaf, (b) vaping tobacco containing nicotine and (c) vaping a combination of cannabis leaf and tobacco containing nicotine. All participants will vape each product with the PAX loose-leaf vaporizer.

PAX vaporizers will be purchased by the study team. The cannabis leaf will be obtained through the National Institute on Drug Abuse Drug Supply Program. The tobacco containing nicotine, used in conditions (b) and (c) will come from commercially available Marlboro brand cigarettes. The same amount of cannabis or tobacco will be used in all conditions.

The study will be conducted during three outpatient visits separated by at least 48 hours. The order of treatment (cannabis leaf, tobacco with nicotine, cannabis leaf & tobacco with nicotine) will be counterbalanced between subjects. Subjects will be blinded to the content of the vaporizer on the study day but will be told during screening that they will vape cannabis alone, tobacco alone, and cannabis plus tobacco with nicotine.

1.4.2 Number of Subjects

A total of 14 subjects will be enrolled in this study over a period of about 6 months. The anticipated accrual rate is approximately 2-4 subjects per month.

1.4.3 Study Timeline

- Study application was submitted to the Institutional Review Board (IRB): pending
- IRB Approval date: June 14, 2018
- Other approvals:
  - Research Advisory Panel of California: Approved
  - Schedule 1 license from the US DEA: Received
  - Investigational New Drug Application: Approved

1.5 ELIGIBILITY

All individuals interested in participating and who meet the inclusion/exclusion criteria will be invited to be part of the study. Inclusion criteria for participants to be enrolled are described below. Eligibility will be assessed by the Clinical Research Coordinator beginning an eligibility checklist at the time of the online survey. This checklist will be updated during the phone screen and finally after the in-person screening visit.

1.5.1 Inclusion Criteria

- Age ≥21 years ≤ 70 years
- Regular user of combustible tobacco cigarettes (at least 1 cigarette weekly)
- Regular user of cannabis in any form administered through the pulmonary route (smoking and/or vaping) at least once a week.
- Positive for THC on screening toxicology test
- Willing to abstain from tobacco smoking and all other combustible products (ex: cigars) for 12 hours prior to each outpatient hospital admission.
- Willing to abstain from smoking/ingesting cannabis for 12 hours prior to each outpatient hospital admission.

- Willing to abstain from using any kind of nicotine products for 12 hours prior to each outpatient hospital admission (ex: electronic cigarettes, nicotine replacement therapy).
- Saliva cotinine ≥ 30 ng/mL and/or NicAlert of 6
- Healthy (based on limited physical examination and medical history collected during screening)
  - Heart rate < 105 BPM
  - Systolic Blood Pressure < 160 and > 90 [*considered out of range if both machine and manual readings are above/below these thresholds*]
  - 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
  - Women of child-bearing potential must use an acceptable contraceptive during the study

1.5.2 Exclusion Criteria

- Any congenital or acquired immunologic disorders due to the following:
  - Human immunodeficiency virus [HIV] infection
  - Congenital immune deficiency syndromes
  - Chronic diseases (diabetes mellitus, cancer, emphysema, or cardiac failure)
  - Intensive Care Unit care
  - Malnutrition
  - Immunosuppressive therapy of another disease process (e.g., radiation, cytotoxic chemotherapy, anti-graft rejection medication, corticosteroids, monoclonal antibodies directed against a specific component of the immune system)
- Medical (The following unstable medical conditions):
  - Heart disease
  - Seizures or history of seizure disorder
  - Cancer
  - Thyroid disease (okay if controlled with medication)
  - Diabetes
  - Hepatitis B or C or Liver disease
  - Glaucoma
  - Kidney disease or urinary retention
  - History of stroke
  - An ulcer in the past year
  - Active use of an inhaler for Asthma or COPD
  - History of traumatic brain injury with current sequelae
  - History of paranoia after marijuana use

- Psychiatric conditions
  - Current or past schizophrenia, and/or current or past bipolar disorder
  - Major Depression (current or within the past year)
  - Major Personality Disorder
  - Participants with current or past minor or moderate depression and/or anxiety disorders will be reviewed by the study physician and considered for inclusion
  - History of 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 and are currently abstaining from drug and alcohol
  - Positive toxicology test for illicit drugs at the screening visit (THC & prescribed medications okay)
  - Opioid Replacement therapy (including methadone, buprenorphine)
  - Scoring a 7 or higher total sum score on the Severity of Dependence Scale for cannabis use.
- 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.
- Other Medications
  - Use of medications that are inducers of nicotine metabolizing enzyme CYP2A6 (Example: rifampicin, carbamazepine, phenobarbital, and other anticonvulsant drugs).
  - Concurrent use of nicotine-containing medications
  - Any stimulant medications (example: Adderall) generally given for ADHD treatment
  - Use of sympatholytic medications for cardiovascular conditions including hypertension (Example: beta and alpha-blockers)
- Other/Misc. Chronic Health Conditions
    - Oral thrush
    - Fainting (within the last 30 days)
    - Other “life threatening illnesses” as per study physician's discretion
- 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

- Pregnancy
    - Pregnancy (self-reported and urine pregnancy test)
    - Breastfeeding (determined by self-report)
- Concurrent participation in another clinical trial
- Inability to communicate in English
- Planning to quit smoking or cannabis use within the next 60 days

1.6 ID AND RANDOMIZATION

1.6.1 Study ID Assignment

Subject IDs will be assigned as follows: XXXX-YYY, where XXXX is the CTSI CRS Study Number and YYY is assigned sequentially once a subject consents to the study during the Screening Visit, starting with XXXX001. Plasma samples and inpatient questionnaire labels will be labeled as follows: XXXX-#-YYY, where # is the study day (1 for day 1, 2 for day 2, 3 for day 3).

1.6.2 Subject assignment to conditions

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Study Day 1	C	T	C+T	C	T	C+T	C	T	C+T	C	T	C+T	C	T
Study Day 2	T	C+T	C	T	C+T	C	T	C+T	C	T	C+T	C	T	C+T
Study Day 3	C+T	C	T	C+T	C	T	C+T	C	T	C+T	C	T	C+T	C

*Where, C is cannabis leaf; T is tobacco cigarettes; C+T is cannabis leaf + tobacco cigarettes. Order of enrolled subjects will be counterbalanced; order is assigned at admission.

1.7 PARTICIPANT WITHDRAWAL

1.7.1 Dropouts and compensation

If a participant declares they are no longer interested in completing the study, they will be considered a “dropout.” If the participant decides to stop participating in the study prior to outpatient admission for study day 1, they will only receive compensation for the Screening Visit (i.e. $30).

- Complete study day 1: $100
- Complete study day 2: $100
- Complete study day 3: $100
- For complying with all study procedures including attending the orientation visit, abstaining from tobacco cigarettes, nicotine products, and marijuana use 12

hours prior to Study Days 1, 2 and 3, subjects will be given an additional $120 bonus ($40 each day).

- Total possible compensation is $450.

1.7.2 Lost to Follow Up

If a participant is unable to be contacted and does not respond to calls from the Clinical Research Coordinator (up to three unsuccessful phone contact attempts), he/she will be considered "lost to follow-up" (LTFU). Before a participant is considered LTFU, every effort will be made to contact him/her. After being considered LTFU no further outreach will be conducted. If a formerly LTFU participant re-contacts the CRC outside a given study window, participant will be rescheduled for screening.

2 STUDY TIMELINE

2.1 VISIT SCHEDULE & WINDOWS OF ASSESSMENTS

Assessment Point	Maximum Time from REDCap Questionnaire Screen
REDCap Questionnaire	
In-Person Screening Visit	14 days from REDCap questionnaire
Orientation	45 days* (~1 month from in-person screening)
Study Day 1	47 days
Study Day 2	49 days
Study Day 3	51 days

*In-person screening may be repeated if this window is exceeded.

3 STUDY VISITS AND PROCEDURES

3.1 REDCap Questionnaire

Interested participants will fill out a short (10-minute) survey on REDCap. The CRC will complete an eligibility checklist, beginning at the time of this online survey. This checklist will be labeled first by the REDCap ID and later by the Study ID after consent & assignment. The Clinical Research Coordinator (CRC) will then determine if the participant is eligible to attend a Screening Visit based on above inclusion/exclusion criteria.

3.2 Phone Evaluation & Confirmation

3.2.1 Phone Evaluation Scripts

Various items related to eligibility must be confirmed by the CRC during a phone conversation.

If preliminarily eligible, the CRC will contact the participant by phone and ask them the following questions:

Script: "*Okay, I am going to ask you various questions about your medical history. This will help us determine if you are a good match for our study. Do I have your consent to ask these questions?"*

"1) *Have you ever been diagnosed with or told you have any of the following disorders? I'll read a list aloud and you at the end, just let me know yes or no."*

a) *Human immunodeficiency virus infection (or HIV/AIDS)*
b) *Congenital immune deficiency syndromes*
c) *Chronic diseases, such as diabetes mellitus, cancer, emphysema, or heart failure?*

*If yes to a-c, participant is ineligible. End the phone screen.

2) "Have you ever acquired a disorder from any of the following?"

a) *Being in Intensive Care Unit (ICU) care*
b) *Malnutrition*
c) *Immunosuppressive therapy (examples of these may be radiation, cytotoxic chemotherapy, anti-graft rejection medication, corticosteroids, monoclonal antibodies directed against a specific component of the immune system)*

*If yes to a-c, participant is ineligible. End the phone screen.

3) "Have you ever experienced a traumatic brain injury, or currently experiencing any symptoms resulting from a head injury?"
*If yes, participant is ineligible. End the phone screen.

4) "Do you have a history of feeling paranoid after using marijuana"
*if yes, participant is ineligible. End the phone screen.
5) Do you currently take any medications?

*If a psychiatric medication is a non-SSRI or SNRI, or participant is on anticonvulsants, nicotine replacement therapy, stimulant medication, opioid replacement therapy or beta-blockers, participants is ineligible.
*Review any other questionable medications with the PI/Study Doctor.

6) Are you willing to abstain from tobacco smoking, smoking any other tobacco products

(like cigars, cigarillos, blunts, splits & other) from smoking or ingesting and cannabis or

marijuana products, and from using nicotine products of any kind (like e-cigarettes, or nicotine gum, patch, lozenge, inhaler) for 12 hours before each of your study days?

*If no, ineligible.

7) ***If female****,* for the duration of this study, are you willing to use an acceptable method of birth control if you have sexual intercourse with a man? Acceptable methods are barrier methods, hormonal methods, or implantation devices. Please let me know, yes or no. *If no, ineligible.

8) **If participants** indicate they are in a drug treatment program & further clarification is needed, *"I saw you indicated that you are in a drug treatment program. Can you let me know what that is for? Did you complete it or are you currently in the program"*

*If recently completed a program, they are eligible. If still in the program, ineligible.

If still eligible after those questions, a Screening Visit appointment should be scheduled immediately.

3.2.2 Scheduling Script

V-PAX Phone Screen & Consent Conversation

If preliminarily eligible based on the REDCap report, contact the participant by phone and ask them the following questions using the script:

Study Team: Good afternoon, may I please speak with [name]?

If the Person is not available: Thank the person who answered and say goodbye.
If the Person is available: First confirm that you are speaking to the correct person.

Study Team: This is [name] calling from the UCSF Tobacco Research Center. I am a coordinator working with Dr. Benowitz's research group.

Is this an Ok time for you to speak?
If the Person says "No" or "I'm not sure"

Study Team: Okay. [Ask if you can schedule another time to talk. If the person is not sure or seems hesitant, thank him/her and say goodbye.]

If the Person says “Yes”

Study Team: Great. I wanted to talk with you about a new study for tobacco cigarette and cannabis smokers who are willing to vape cannabis, tobacco and a combination of the two using the PAX loose leaf vaporizer. You may remember you filled out a questionnaire online to be considered for this study. You indicated that you were interested in learning more.

If the Person says “No” or “I’m not sure”

Study Team: No problem. I just wanted to make sure you had the opportunity to learn about any study we have at the UCSF Tobacco Research Center. Thank you for your time.

If the Person says “Yes”

Study Team: Study Team: This new study is looking at the safety and addictiveness of orally vaping cannabis (THC) and nicotine. This study consists of 5 visits across about 14 days. First, there is a 45 minute screening visit at our research center, to make sure you are a good match for our study. Then you will return for a 30 min orientation visit the day before your first study visit. For each outpatient study visit, you will be admitted for 8 hours in the hospital starting at 7am and will be discharged from our hospital research ward at ZSFG at 3pm. Each of your 3 outpatient study visits will involve blood draws, urine collections, pulse monitoring (heart rate) & questionnaires.

That’s the purpose and procedures for our study. Can I answer any questions? (if yes, answer questions; if no continue…)

Okay, the first step is for me to ask you some questions to see if you are a good match for the study. This can take about 20 minutes. Do you have the time right now to speak with me? Do I have your consent to ask these questions?”

Update the Eligibility Checklist as you ask the questions.

Study Team: (if no) “Okay, well it seems like this study may not be the best fit for you, which is totally fine. Would you like us to keep your name down for other studies as they come up?”

(If yes, continue)

Study Team: “Okay, so we reviewed the purpose and procedures of this study. I’d like to let you know that research is 100% voluntary and you can choose at any time not to participate.”

“I’d like to review some risks with you

We will be collecting blood so there is a risk of pain, swelling, bruising, or infection at the draw site. Some people experience feelings of paranoia after smoking marijuana, so we will dismiss you from the study if you develop feelings of paranoia. Study procedures may be inconvenient and tedious. For example you will befilling out many forms, spending time in the hospital, providing specimens, etc. We will also ask you to abstain from tobacco cigarette use, so you may feel uncomfortable, irritable, restless or have difficulty concentrating due to possible nicotine withdrawal. Nicotine withdrawal may also result in headaches, nausea, fatigue, or changes in mood. We will also be measuring your blood pressure and it may feel uncomfortable depending on the tightness of the cuff. And finally, we will be collecting personal information from you, so there is a risk of breach of confidentiality. However, we will do our best to keep your confidentiality. There may be undiscovered drug toxicity associated with the use of cannabis, that can put you at risk for unknown effects. There may be long-term effects associated with the use of cannabis that are currently unknown to the scientific community.

Can I answer any questions about risks?

Okay, let's talk about the benefits. There are no direct benefits to you, but you will be helping us learn about how safe and addictive it can it is to vape cannabis and nicotine, which has great potential benefit to other smokers like you.

Here are some important reminders: You will be asked to abstain from any type of cannabis use from 6pm (approximately 12 hours) prior to each hospital admission. This cannabis use includes smoking cannabis, vaping cannabis, edibles, THC concentrates, etc. You will also be asked to abstain from recreational drug use from the time of orientation until the study is completed. You will be asked to abstain from the use of other tobacco products that include cannabis for approximately 12 hours prior to each hospital admission. This includes blunts and spliffs. You will be asked to abstain from using any type of tobacco and nicotine products from 6pm (approximately 12 hours) prior to each hospital admission. This nicotine use includes cigarettes, e-cigarettes, smokeless tobacco, pipes, cigars and cigarillos.

Please note that there are no guest are permitted at the hospital. This is to protect everyone's confidentiality.

We will also be compensating you for your time and effort – if you complete all parts of the study, you will receive a total of $450 via check. You will fill out a check request after you complete each portion of the study and it is estimated to take 4-6 weeks to receive it.

Can I answer any other questions? (if yes, answer) (if no proceed)

Okay, can I ask you a few questions?

Do you remember – how long does this study last? (about 14 days) Do you remember – how many visits will you have? (5 visits)

What are some risks you may experience? (discomfort, bruising, mood changes, breach of confidentiality, etc)

Do you think you are interested in seeing if you are a match for the study?
(if yes) “Great! I am going to send you a powerpoint presentation via your email. Please look it over – it describes in great detail more information about the study. I will also send you the consent form – please take time to read it over and review carefully. If you agree to participate, you will be prompted to sign the form.

I can schedule you for the next phase of screening – this is the 45 minute screening visit I mentioned to you. When would be a good time for you to come in for that?
(proceed with scheduling visit)

Okay, very important before you come in…
After you sign the consent form and about 24 hours before your visit, I will send you a survey link to your email. It’s important that you complete this survey before you come in, otherwise you will need to complete it in person and the visit will take longer than 45 minutes.

At the screening visit we will first review a HIPPA form. This is another important form for you to sign related to the study and your health information privacy. We will then have you fill out a medical history form and we will conduct a quick interview and collect your basic vitals and a saliva sample. At this visit, you will also need to provide a urine sample for a drug test and a pregnancy test, if applicable. The drug test must be positive for THC and negative for all other drugs. If your positive for any drugs other than marijuana it will result in an automatic dismissal without payment. There will also be a breath measurement to assess your tobacco cigarette smoking status. If this measurement shows you are not a smoker, we will dismiss you without payment. If you pass these tests and complete the screening visit we will compensate you with a $30 check, which will reach your home within 4-6 weeks.

For this visit, please bring in your photo ID to verify your name and age. If you are currently taking any medications, please bring the bottle or a copy of your prescription, so we can verify any medications you are taking. If you need to reschedule your study visit, we will give you one option to reschedule, so please make sure you pick a time that works with your schedule.

Any other questions?
(if no) GREAT! I will send you a confirmation email which will include the PowerPoint summary and consent form. Please do not hesitate to contact me with any questions.

3.2.3 Email Confirmation

Participants will receive a confirmation email upon scheduling their screening visit.

Hi [participant name],

Thank you for your interest in helping us with our Vaping Tobacco and Cannabis Study.

This email is to remind you that you are now scheduled to come in for your visit on [DAY, DATE at TIME].Our center is located at Zuckerberg San Francisco General (1001 Potrero Ave) in Building 100 on the 2nd floor. The directions are as follows: Turn onto 22nd Street from Potrero Avenue towards the brick ZSFG buildings. Continue on 22nd Street and you will see Carr Auditorium at your 3rd right. Walk through the parking lot and enter Building 100 through the grey door. You will see signs directing you to UCSF Tobacco Research Center.

Please ring the door bell to notify us that you are here. We do ask that you don't bring any guests with you since our center cannot accommodate unscheduled visitors.

Please remember to bring with you:
- A valid Photo ID
- Your prescription medication bottles, if you have any
- A pack of your cigarettes to confirm your brand usage

To note:
- Be prepared to provide urine for a drug test.
- The screening visit will take around 45 minutes.
- You will be compensated $30 for your visit via mailed check, which can take up to 4-6 weeks to reach you after your visit, as long as our test shows you are a smoker of tobacco cigarettes.

Please feel free to email us if you have any questions or need to reschedule (tobaccocoord@ucsf.edu). Thank you again for your help and we look forward to seeing you!

3.3 SCREENING VISIT PROCEDURES

Subjects will undergo a 45 min Screening Visit to obtain and determine their enrollment eligibility. During this visit, participants will complete a basic physical assessment (height, weight, heart rate, blood pressure, expired carbon monoxide, urine drug test, and pregnancy test (if applicable), saliva collection, and questionnaires: the Severity of Dependence Scale, THC use history and a standard screening packet asking demographics, health history and other product use.

The CRC will determine initial eligibility via basic physical assessment, toxicology screen, and inclusion/exclusion criteria. In the event of a positive toxicology test (except marijuana), subject will be dismissed immediately without payment and the remainder of the screening visit measures will not be completed. Participants who fail the pregnancy test, blood pressure test, or BMI assessment will be paid and dismissed. Clinical Research Coordinator should follow the Tobacco Research Center Pregnancy Test SOP for communicating results with the participant. Participants who indicate an exclusionary medication that they

neglected to report during the initial REDCap survey, will be dismissed without

payment. In all cases of early dismissal, any collection of biosamples will be discarded.

Upon determination of preliminary eligibility, the participant's saliva sample will be delivered to the lab for analysis. Participants must have saliva cotinine levels ≥ 30 ng/mL to be considered eligible for enrollment. NicAlert tests will be used to verify cotinine in cases when saliva cotinine samples are not able to be run quickly.

3.2.4 Consent Process

Upon initiation of the Screening Visit, CRC will initiate the Informed Consent process. The participant will be asked to read the first line of the consent form aloud to ensure reading ability. The CRC will instruct the participant to read each page of the consent document. Participants will be asked to refrain from signing the consent form until CRC returns to discuss consenting document specifics. CRC will leave the room for 10 minutes to allow subject to read the consent form. After 10 minutes, CRC will return, answer any questions, and present a brief PowerPoint presentation highlighting important aspects of the consent document. The CRC will ask the participant if they have any questions, and will ask them questions to verify understanding. Consent will be obtained via participant's and CRC's signature at the conclusion of the PowerPoint presentation. Two original consent documents will be signed by both the participant and the CRC. One is to be filed and stored in the participant's folder, another is to be given to the Hospital research ward for their records. The CRC will make a copy of one of those consent documents and give to the participants for his/her records. CRC should present participant with a copy of their Bill of Rights as a research participant at UCSF. Participant will also be presented with the HIPAA authorization form to sign after an explanation of what it entails. The HIPPA form must have "entire medical record" checked off in Section B, information pertaining to drug & alcohol abuse checked off in Section C, and the optional activities of banking samples checked off & initialed in Section G.

3.2.5 Forms for Data Collection

During recruitment participants will complete the following below.

1. REDCAP Online Screen
2. Phone Screen Evaluation

At Screening participants will complete the following below.

The Screening Packet consists of the following forms:

3. Personal Data Form

4. Demographic Information
5. Nicotine/Tobacco Product Use Form
6. Electronic Cigarette or E-Cigarette History
7. Penn State E-Cigarette Dependence Index
8. E-Cigarette Use Assessment
9. Smoking History Screening Form [Cigarettes]
10. Alcohol Use
11. Non-medical Drug Use
12. Medical History
13. Physiological Assessment Form
14. Center for Epidemiological Studies Depression Scale (CES-D)
15. Fagerström Test for Nicotine Dependence (FTND)

Participants will also complete:

16. THC History Questionnaire
17. Severity of Dependence Scale (SDS)

The outpatient questionnaires consist of the following forms:

1. Marijuana Cravings Questionnaire- Short Form (MCQ-SF)
2. Positive Affect Negative Affect Schedule (PANAS)
3. Minnesota Nicotine Withdrawal Scale (MNWS)
4. Modified Cigarette Evaluation Questionnaire (mCEQ)
5. Drug Effect Questionnaire (DEQ-5)

3.3 ORIENTATION

Subjects will be asked to come back to the UCSF Tobacco Research Center for an Orientation Visit at least 48 hours before Study Day 1. This visit will take approximately 30 - 45 minutes. The following will happen during the Orientation Visit:

- A urine sample will be collected and saved.
- Participants will be asked to not use marijuana or marijuana-containing products for 12-hours prior to each study visit.
- Participants will be asked to not use tobacco cigarettes or nicotine-containing products for 12-hours prior to each study visit.
- Participants will be asked to not use any recreational drugs from that point until the study is completed.
- Study procedures will be reviewed with the participants, who will do practice sessions of outpatient questionnaires and gas trap procedure.

3.4 PHARMACOKINETIC STUDY: Outpatient Visits

3.4.2 Protocol for Outpatient Study

3.4.1(a) Marijuana preparation

Cannabis leaf material (11.7% THC) obtained from NIDA will be stored frozen in a locked room in the Zuckerberg San Francisco General Hospital Pharmacy. When a participant is randomized, the pharmacy will dispense of 250 mg of cannabis (this includes a back-up supply of 125 mg). All cannabis will then be stored in the freezer compartment of the medication refrigerator in the medication room of the Clinical Research Services Ward 5B.

Cannabis material to be used by a study participant will be humidified 24-36 hours before use. Using a petri dish placed at the bottom of the desiccator, 2 centrifuge tubes, each filled with sodium chloride solution, will be emptied into the dish. Cannabis cigarettes will be placed on the desiccator platform and maintained at room temperature overnight, which is expected to raise the moisture of the cannabis cigarettes by 3 to 5%. Cannabis material will be used within one hour after removal from the humidifier.

3.4.1(b) Hospital Admission Protocol

Before arrival to the hospital, the study co-I or CRC will meet the participant to collect a urine sample for drug testing. Only when it is confirmed that the participant is negative for all drugs other than cannabis, will we admit him/her on the research ward.

Upon arrival at the research ward, the following procedures will occur:

1. Nurses will ask the participant when they last smoked, vaped, or used THC.
    - If the participant smoked cigarettes or vaped e-cigarettes after 10pm the night before either admission, they will be dismissed from the study.
2. An expired CO test will be administered. If their CO reading is greater than or equal to 5 ppm, they will either be dismissed from the study or procedures will be delayed depending on PI discretion.
3. A pregnancy test will be administered to female participants. If the pregnancy test is positive, they will be dismissed from the study.
4. If the participant is female, the pregnancy test will also serve as the voided urine. If the participant is male, they will provide urine sample for discard.

3.4.1 (c) Outpatient Study Protocol

Samples	Time	Activity
		STUDY DAY 1 (same procedures as Study Days 2 & 3)
	~7 AM	• Nurses will measure and record the room temperature. • Subject arrives at about 7 AM • Nurses will ask the participant when they last smoked, vaped and used marijuana • Expired CO measured: If <5 ppm, then admit; if ≥ 5 ppm, then dismiss • Urine pregnancy test and drug toxicology test (if applicable), positive result then dismiss (if female this can the voided urine) • If male, participant voids urine, the discards • Subject's personal e-cigarette and other tobacco products are taken away at admission • No product until 8:30 AM
	~7:30	• Participant rests and eats a light breakfast, may drink decaffeinated coffee or tea • Liquids (water) will be given in preparation for urine sample
US#1 (Urine sample) **BS#1 (blood sample)**	~8:20	**Pre-STANDARDIZED Cannabis Vaping (pre-SVC)** **PAX device filled with 125 mg of grounded cannabis leaf containing about 12% THC by the study team and weighed using microbalance** ***NOTE: The order of the first condition will not be the same between subjects. The order here is shown for the first participant.*** • After resting (before IV catheter insertion), baseline urine sample will be collected • IV placed (plastic catheter in vein of forearm) **Baseline Questionnaire Packet # 1, after IV placement** • Weigh PAX device containing cannabis before vaping • BLOOD sample #1 (Pre-EC1) collected before standardized session • BLOOD sample, catecholamines • *Blood sample should be taken just before first standardized session; ~8:20 AM* **BASELINE Heart Rate, by pulse oximeter, baseline skin temperature, baseline core body temperature**

SCV	~8:40-8:45	**C STANDARDIZED SESSION (Standardized Cannabis Vaping) -One (1) 5 second puff every 45 seconds for a maximum of 3 puffs with each puff followed by a 10 second breath hold.** • PAX will be turned on and allowed to pre-heat at temperature setting #2, which heats at about 193 °C. • Subjects will be voice-prompted (taped or in-person by CRC) • Gas trap procedures will be conducted (See Section 3.5.2) • The PAX device will be collected for weighing.
2-min **BS#2**	~8:47	**2-MIN Post-SCV; Blood Sample #2** • BLOOD sample #2 collected after the SCV session • Heart Rate
5-min **BS#3**	~8:50	**5-MIN POST-SCV; Blood Sample #3 and Questionnaire Packet #2** • BLOOD sample #3 (5-min after last puff) • BLOOD sample, catecholamines • 5-min HEART RATE, 5-min SKIN TEMPERATURE TEST, Core body temperature • Questionnaire packet between 5-min and 15-min blood sample. CRC will administer.
	~8:55	**10-min HEART RATE** • Questionnaire packet #3
15-min **BS#4**	~9:00	**15-MIN POST-SCV; Blood Sample #4** • BLOOD sample #4 (15-min after last puff) • 15-min HEART RATE, 15-min SKIN TEMPERATURE TEST, Core body temperature • Questionnaire packet #4
	~9:05	**20-min HEART RATE** • Questionnaire packet #5
	~9:10	**25-min HEART RATE** • Questionnaire packet #6
30-min **BS#5**	~9:15	**30-MIN POST-SCV; Blood Sample #5** • BLOOD sample #5 (30-min after last puff) • 30-min HEART RATE, 30-min SKIN TEMPERATURE TEST, Core body temperature
45-min **BS#6**	~9:30	**45-MIN POST-SCV; Blood Sample #6** • BLOOD sample #6 (45-min after last puff)
55-min	~9:40	• Questionnaire packet #7
	~9:45	**60-MIN POST-SCV; Blood Sample #7**

1-h **BS#7**		• BLOOD sample #7 (1-h after last puff) • 1-h HEART RATE, 1-h SKIN TEMPERATURE TEST, Core body temperature
85-min	~10:00	• Questionnaire packet #8
90-min **BS#8**	~10:15	**90-min POST-SCV; Blood Sample #8** • BLOOD sample #8 (90-min after last puff) • 90-min HEART RATE, 90-min SKIN TEMPERATURE TEST, Core body temperature
2-h **BS#9**	~10:45	**120-MIN POST-SCV; Blood Sample #9** • BLOOD sample #9 (120 min after last puff from THC1) • 2-h HEART RATE, 2-h SKIN TEMPERATURE TEST, Core body temperature
3-h **BS#10**	~11:45	**180-MIN POST-SCV; Blood Sample #10** • BLOOD sample #10 (180 min after last puff) • 3-h HEART RATE, 3-h SKIN TEMPERATURE TEST, Core body temperature • Light lunch at noon
6-h **BS#11**	~14:45	**360-MIN POST-SCV; Blood Sample #11 and Questionnaire Packet #4** • BLOOD sample #11 (2 h after last puff) • 6-h HEART RATE, 6-h SKIN TEMPERATURE TEST, Core body temperature • Nurses will administer Questionnaire Packet #9
6-h **US#2**	~14:55	**6-h URINE SAMPLE (6-h post SVC)**

End of Study Day 1

Collect all of subjects' products.

Before each discharge, participants will be evaluated by the study physician and administered the Drug Effects Questionnaire. Participants who drive to the research ward, must report a zero "0" on the VAS of drug effects before discharge. If participants took public transportation to the hospital, they must score a 50 or less on the VAS of drug effects.

Discharge with the following instructions:

1. Abstain from smoking marijuana or using marijuana products 12 hours prior to your next admission.
2. Abstain from tobacco products and any nicotine products 12 hours prior to your next admission.
3. Arrive at hospital at 7:00 AM on scheduled second visit.

Repeat all procedures above for Study Day 2 with the alternate product "T" (tobacco containing nicotine) and the following standardized vaping: **One (1) 5 second puff every 45 seconds for a maximum of 3 puffs with each puff followed by a 10 second breath hold.** PAX will be filled with 125 mg of tobacco from American Spirit Blue cigarettes.
Repeat all procedures above for Study Day 3 with the alternate product "C+T" (125 mg of cannabis leaf + 125 mg of tobacco containing nicotine from American Spirit Blue cigarettes) and the following standardized vaping: **One (1) 5 second puff every 45 seconds for a maximum of 3 puffs with each puff followed by a 10-second breath hold.**

Abbreviations: BS = blood sample; C=cannabis leaf; SCV=standardized cannabis vaping
UX = Urine sample at screening visit, U0=Urine sample at orientation, US=Urine sample

3.4.2 Protocol for gas trap

1) Install a new 47 mm EPM 2000 Whatman filter into the filter cassette.
2) Insert a new clean mouthpiece in the inlet of the filter cassette
3) Connect the filter to the pump and adjust the flow rate through the filter to 10-15 LPM.
4) Have the subject exhale into the mouthpiece with the vacuum pump on.
5) After the 3-puffs, remove the filter to a silanized 16X125 mm glass extraction tube.
6) Transport the container to the Clinical Pharmacology Lab Room 105.

3.4.3 Timing of Blood Collection

Blood Spec #	Event	Time of day	Nic/Cot [6 ml]	THC [6 ml]	Catecholamines [6 ml]	Total VOLUME drawn	Notes
STUDY DAYS 1, 2 & 3							
B1	Pre-SVC	8:20	6	6	6	18	6ml green top Hemogard tube for all
B2	2-min post SVC	8:47	6	6		12	
B3	5-min post SVC	8:50	6	6	6	18	

B4	15-min post SVC	9:00	6	6		12	
B5	30-min post SVC	9:15	6	6		12	
B6	45-min post SVC	9:30	6	6		12	
B7	60-min post SVC	9:45	6	6		12	
B8	90-min post SVC	10:15	6	6		12	
B9	120-min post SVC	10:45	6	6		12	
B10	180-min post SVC	11:45	6	6		12	
B11	360-min post SVC	14:45	6	6		12	

3.4.4 Timing of Saliva Collection

Saliva Spec #	Event	Time of day	COT	Notes
S-0	Screening visit	N/A	5 mL collected	Cotinine testing

3.4.5 Timing of Urine Collection

Urine Spec #	Event	Time of day	Total VOLUME Collected (mL)	Notes

UX	Screening visit	N/A	~50	Toxicology and pregnancy test; remaining discarded
U0	Orientation	N/A	~50	Baseline urine sample collected
U1, U3 & U5	Pre-EC1 loading	7:00	~50	Days 1, 2 & 3
U2, U4 & U6	Post 6-h THC1 loading	14:55	~50	Days 1, 2 & 3

3.4.6 Sample Assays

- Plasma: nicotine, cotinine, 3-Hydroxicotinine (3HC)
- Urine: total nicotine metabolites (nicotine equivalents), NNAL, catecholamines, mercapturic acid, biomarkers of acrolein and propylene oxide, and other volatile organic compounds (VOCs).

4. 5B PAPERWORK AND PREPARATION FOR OUTPATIENT STUDY

- **Admission Request Form**
  - Use the current template for this form
  - Participant, date of admission (night before)
  - Address/phone number/DOB/SSN
  - Sent via PHI secure email (This is done after confirmation of the hospital and participant that this is the correct date) (Re-submit with updated date as needed)
- **Coversheet**
  - Use the current template for this form
  - Participant name and study ID on top as a label.
  - Edit date of admission and date of drop-off
  - General info about the study prepped on a per patient basis during admission
- **Flow Sheet (one long continuous document)**
  - Template existing & Study Staff and 5B review this at study initiation
  - Update this with e-cig brands/liquid info
  - Explain on the flow sheet the hospital will put PHI on this, we copy without PHI and file
- **Outpatient Form**
  - Make copy to 5B and we have the original in our chart
- **MD Orders**

    - Pre-signed
    - Name on the top corner and name/date **IN PENCIL**
- **Admit PE**
    - Name **IN PENCIL** at the top
    - Fill out by Sara/Delia at the time of the visit
- **Adverse Event Form**
    - Initialed if none occurred
- **Setup**
    - Should be done within 3 days before the admission and given to 5B within a day of the admission if possible.
    - Documents should be given to 5B in the order above
    - Paper clipped and given to them
    - 5B will make/use labels
    - Questionnaire Packet, organized and clipped by day
    - Consent form (there will be 3 signed at screening). **The original for 5B will go in the set-up**.

- At completion, CRC will copy de-identified:
    - Flowsheet
    - MD Orders
    - Admit PE
    - Discharge Sheet
    - AE Form (we take the original)

5 ADVERSE EVENTS & PROTOCOL DEVIATIONS

5.1 SAFETY MONITORING

During the outpatient stay, subjects will be monitored by the Clinical Research Coordinator and 5B staff who will directly contact the study physician in case of any subsequent adverse events. If the subjects experience serious adverse effects, the research staff will evaluate this with them and decide if they should be withdrawn from this study.

5.2 DEFINITION OF ADVERSE EVENTS

5.2.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding),

symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

5.2.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

5.2.3 Suspected Adverse Reaction

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

5.2.4 Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the investigator brochure or package insert(s), or listed in the consent form, or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

“Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered unexpected for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

5.2.5 Serious Adverse Reaction

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

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

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

5.2.6 Life-threatening Adverse Events

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

5.3 REPORTING ADVERSE EVENTS

Reporting of serious adverse events will follow the current requirements of the Committee on Human Research (CHR). Specifically, the following will be reported within five (5) working days of the PI's 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 Principal Investigator 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 advents from phlebotomy, study drug, or other study procedures:

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

The supervising study physician will be notified of all grades 2 through 5 AEs. Additionally, Dr. Benowitz will be notified of all grades 4 and 5 AEs.

5.4 PROTOCOL DEVIATIONS AND 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. For example, if a participant was enrolled in the study but they were under the age of 12 or they were enrolled without consent of a parent. Protocol violations will be recorded on a protocol violation sheet, reviewed and signed by the PI and reported to the CHR.

6 DATA COLLECTION AND MANAGEMENT

6.1 DATA COLLECTION FORMS

Data Collection Forms entered by participants include:

1. Screening packet, except Physiological Assessment Form
2. REDCap Questionnaire
3. Research Ward Outpatient Questionnaire Packets 1-10

Data Collection Forms entered by Research Staff:

1. Physiological Assessment Form of the Screening Packet
2. Outpatient Product Weight Record

6.2 DATA ENTRY, STORAGE, AND ANALYSIS

A folder "**XXXX ECig THC**" on the shared drive utilized by the Clinical Pharmacology Lab will be used to store electronic data from this study (where XXXX is the CTSI-CRS study number).
All databases are password protected with the following: **XXXXTHC**

1. Information collected from messages in the REDCap questionnaires will be entered by CRC in the **Call Log** database
2. A record of participants screened and/or enrolled is kept by CRC using the **Participant Log**
3. Personal data and Demographic data from the Screening Packet are entered by the CRC in the **Personal Data & Demographics database**
4. Information entered by the participant on the Screening Packet are entered in the **Screening Database** by the CRC
5. Data collected during the outpatient days, except questionnaire data, are entered by CRC in **Outpatient Measures**
6. Questionnaire data from the Inpatient days are entered by the CRC in **Outpatient Questionnaires**

6.3 DATA ANALYSIS

The study is not hypothesis-driven but will provide valuable data to guide future research as well as provide needed data on THC delivery and effects from vaping. Variables of interest include amount of THC inhaled, amount exhaled, and amount retained; pharmacokinetic parameters for THC, 11-OH-THC, and nicotine, the psychoactive compounds; heart rate and blood pressure change; and subjective effects.

Delivered and Retained Doses: Delivered THC and nicotine doses are estimated as the change in e-cigarette weight × concentration of THC or nicotine in e-liquid. The amount of THC or nicotine systemically retained is estimated as delivered dose minus amount in gas traps.

THC, 11-OH-THC, and Nicotine Pharmacokinetics: Pharmacokinetic parameters will be estimated from blood THC and 11-OH-THC and plasma nicotine concentrations using Phoenix WinNonlin 6.3 (Pharsight Corporation, Mountain View, CA). Time to max concentration (T_{max}), max concentration (C_{max}), and area under the blood/plasma concentration-time curves (AUC) will be estimated using a non-compartmental model and trapezoidal rule. C_{max}, and $AUC_{0\rightarrow\infty}$ will be adjusted for baseline nicotine levels.

Averages and 95% confidence intervals will be computed by e-liquid type (THC only or

THC+nicotine). Although this study is not hypothesis-driven, we will use mixed model analysis of variance (ANOVA) to assess differences in these variables between e-liquids type. Models will include sex as a covariate.

7 DUTIES AND RESPONSIBILITIES OF STAFF

7.1 PRINCIPAL INVESTIGATOR

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

7.2 Study Doctor

The Study Doctor will hold privileges at the CTSI Ward 5B, and will be on call for any serious events that may occur with study participants. They will also be a resource for reviewing medical history, medications, eligibility, or any questions that may pertain to participant eligibility and safety. In some cases the Study Doctor role may be filled by the Study Principal Investigator, Dr. Neal Benowitz.

7.2 CO-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.

7.3 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.

7.4 CLINICAL RESEARCH COORDINATOR

The CRC will oversee study logistics including logging specimens, chart reviews, protocol review, consenting, Screening Visit procedures, scheduling, and orientation procedures.

8 STUDY MANAGEMENT

8.1 PRE-STUDY DOCUMENTATION

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with good clinical practice and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until all approvals have been secured.

8.2 INSTITUTIONAL REVIEW BOARD APPROVAL

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

8.3 INFORMED CONSENT

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation.

8.4 CHANGES IN PROTOCOL

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by the CHR prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

9 PROTECTION OF HUMAN SUBJECTS

9.1 PROTECTION AGAINST RISKS

All subjects will be under close medical supervision of the CRS staff and study doctor. Furthermore, all study procedures will be subject to the approval of UCSF IRB. Patient confidentiality will be maintained as carefully as possible. Authorization for disclosure of protected health information for research purposes will be required in accordance with HIPPA regulations. Patients will be informed that all efforts will be made to keep personal information confidential, however, absolute confidentiality cannot be guaranteed. Patients will be informed that their

protected health information may be disclosed if required by law. All of this will be presented in the informed consent document and authorization for disclosure form.

10 REFERENCES

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APPENDIX A: DATABASE GUIDE

Screening Visit

1. Screening Log

   The Screening Log is a list of all participants who came into the 20th street Tobacco Research Center or ZSFG location for a screening visit for the V-PAX 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: 7845 V-PAX
   - Sub-folder 1: Databases
   - Subfolder 2: Logs
   - name: V-PAX Screening Log
   - Password: 7845THC

2. Saliva Cotinine Screening Log

   The Saliva Screening Log is a list of the cotinine values for participants who came in for a V-PAX screening visit.

   - Location: s-Drive
   - Folder: Clinical Research
   - Sub-folder 1: Screening Log
   - Subfolder 2: 7845 V-PAX
   - name "7845 V-PAX 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: 7845 V-PAX
   - Sub-folder 1: Databases
   - Subfolder 2: Logs
   - name: V-PAX Screening Log
   - Password: 7845THC

4. V-PAX Database

The data collected at the screening visit is located on RedCap under the project titled V-PAX Study Database. This project includes the following forms: Participant Summary Form, Screening Eligibility Checklist, demographic information, Physiological Assessment, protocol violation, con meds, and adverse events. Location: https://redcap.ucsf.edu/redcap_v9.1.13/index.php?pid=21357

5. V-PAX study participant survey Database

The data collected at the screening visit and study visits 1-3 is located on RedCap under the project titled V-PAX study participant survey Database. This project includes the following forms: demographic information, screening packet, SDS, THC Use history questionnaire, NDSS, PS-ECDI, E-WISDOM, E-FTND, CES-D, MNWS, M-CES, PANAS, DEQ-5, MCQ-SF, M-SCALE, VAS.

- Location: https://redcap.ucsf.edu/redcap_v9.1.13/index.php?pid=24277

1. 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: 7845 V-PAX
c. Sub-folder 1: Databases
d. Subfolder 2: Logs
e. name: 7845-V-PAX specimen Log

2. Urine Catecholamine Summary

   The plasma Catecholamine Summary contains the catecholamine data from participants 7845-002-7845-018, including: norepinephrine, epinephrine, and dopamine per volume.

- Location: t-Drive
- Location: t-Drive
- Folder: 7845 V-PAX
- Sub-folder 1: Databases
- Subfolder 2: Logs
- name: 7845-V-PAX specimen Log
- Information is downloaded from ARUP Labs via email from program manager