

Title: Effects of Electronic Cigarette Settings and Liquid Concentrations in Cigarette Smokers and Electronic Cigarette Users

NCT #: NCT03710590

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Document Type: Protocol and Statistical Analysis Plan

Background, Rationale and Goals

1. * Describe the study's background and what is currently known from the scientific literature, including citations, or upload a citation list in document upload. Use lay language whenever possible.

All tobacco products, including electronic cigarettes (ECIGs) are now regulated by the FDA. FDA's "public health standard" requires consideration of how tobacco product regulation will influence risks and benefits to tobacco product users and non-users. These issues are particularly salient for ECIGs due to their increasing popularity (USDHHS, 2016). As the Surgeon General noted, "E-cigarette use among U.S. youth and young adults is now a major public health concern" (USDHHS, 2016, p. vii). Addressing this public health concern through regulation will be challenging because ECIGs are an evolving product class with great variability in nicotine content, device power, and flavors (USDHHS, 2016). These characteristics can influence user behavior including subjective effects, liquid consumption, and nicotine delivery (Hiler et al., in press; Wagener et al., 2017). Also, puffing behavior (i.e., puff topography, including puff number and duration) helps to determine the amount of nicotine delivered to the user and thus ECIG subjective effects (e.g., Hiler, et al., in press). Regulatory action intended to influence ECIG effects must account for these factors. If FDA is to understand how tobacco product regulation will influence the risks and benefits to ECIG users and tobacco cigarette smokers, it may learn much from robust scientific methods that predict the likely population-level impact of potential regulatory action. To understand the benefit of predicting regulatory impact, consider the European Union's (EU's) Tobacco Products Directive 2014/40/EU that limits ECIG liquids to <20 mg/ml nicotine to allow "for a delivery of nicotine that is comparable to the permitted dose of nicotine derived from a standard cigarette...". This directive does not account for variability in product characteristics and user behavior that work against its intent and may increase public health risk. For instance, consider device power: early ECIG models were powered at 10 W or less, but current models achieve 150 W or more (Wagener et al., 2017). Ten puffs from high power ECIGs (mean=70 W) filled with low nicotine concentration liquid (mean=4 mg/ml) can meet and sometimes exceed the nicotine delivery of a tobacco cigarette (Wagener et al., 2017).

Use of these "third generation" ECIGs is on the rise (e.g., Barrington-Trimis et al., 2017) and, relative to lower power devices, they can lead users to consume more nicotine-containing liquid (e.g., Wagener et al., 2017; Etter, 2016). In addition, based on information on e-cigarette forums, individuals are using both low and higher-nicotine concentration liquids (as high as 35 - 50 mg/ml) in their "third generation" devices.

Taken together, these results suggest that, when higher power devices are available, the intended consequences of the EU directive are unlikely to be realized and unintended consequences (more toxicants inhaled) are likely because users can buy high power devices that lead users to consume more liquid, and deliver nicotine more efficiently, even when paired with liquids <20 mg/ml nicotine. The ability to predict the consequences of regulatory action might help FDA craft policies that meet their intent while limiting unintended consequences like these. Indeed, if FDA had scientific methods that could predict these population-level outcomes in advance, these methods could be used to generate objective data to guide the development of potential regulation. Then, by the time data-guided regulations are enacted, they will have been crafted to maximize intended effects and minimize unintended consequences. Our goal is to provide these methods to FDA. To do so, we examine hypotheses related to the effects on user behavior of three potential regulatory actions: limiting nicotine concentration (described here), constraining nicotine flux (nicotine yield/unit time), and reducing flavor availability (these will be tested in other studies). We then use results from the controlled clinical lab testing described here, along with results from other studies, to generate predictions about how these potential regulatory actions might impact the population, and then test our predictions at the population level (in a separate study not described in this protocol).

References:

- Etter JF. (2016). A longitudinal study of cotinine in long-term daily users of e-cigarettes. *Drug Alcohol Depend.* 160:218-21.
- Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N, Shihadeh A, Lopez A, Ramôa C. (in press). Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: The influence of liquid nicotine concentration and user experience. *Experimental and Clinical Psychopharmacology*. *PMC Journal In Process*
- USDHHS (2016). E-cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: USDHHS, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.
- Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E, Leavens EL, Tackett AP, Molina N, Queimado L. (2017). Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control.* 26(e1):e23-e28.

2. * Describe the study hypothesis and/or research questions. Use lay language whenever possible.

The purpose of this study is to determine differences in nicotine delivery, use behavior (puff topography), carbon monoxide delivery, subjective effects, and physiological effects, when cigarette smokers and experienced electronic cigarette users use an electronic cigarette with different settings (different voltage and resistance settings, which together determine power levels) and different e-liquid concentrations.

3. * Describe the study's specific aims or goals. Use lay language whenever possible.

The aims of this study are to better understand how electronic cigarettes with different settings (voltage and resistance, which together determine power levels) combined with liquids of differing nicotine concentrations effect a variety of measures.

This aim involves manipulating liquid nicotine concentration and device power, testing the hypothesis that abstinence suppression, liquid consumption, and nicotine delivery will be lower as nicotine concentration is lowered, but these effects will be offset by higher power. Also, relative to smokers, ECIG users will take longer puffs, thus increasing nicotine delivery and liquid consumed.

4. * Describe the scientific benefit or importance of the knowledge to be gained:

The benefits of this research are of a scientific nature, which should in the long-term benefit society at large. In particular, the use of ECIGs has become increasingly popular, especially among individuals aged 18-24. New regulations are being targeted at this age group and need to be tested in this age group before implementation. The overarching theme of the Center for the Study of Tobacco Products is to provide regulators (FDA and others) with a suite of tools that allow them to test regulations before they are implemented to determine if those regulations will have their intended consequences without causing harm (i.e., unintended consequences). If we cannot study the age group the regulations are targeting, we cannot test potential regulations effectively.

In addition, there is a lack of information about ECIGs and their effects. The results of this study will inform future work regarding the physiological and subjective effects of ECIG use in e-cigarette and cigarette smokers.

5. * Describe any potential for direct benefits to participants in this study:
None.

6. Upload a supporting citation list if applicable:

Study Population

1. * Provide the maximum number of individuals that

1. May participate in any study interaction or intervention (Including screening, consenting, and study activities)

AND/OR

2. You obtain any data/specimens about (regardless of identifiability)

at VCU and at other sites under the VCU IRB's oversight. See the help text for additional guidance.

300

2. If this is a multi-Center Project, what is the maximum anticipated number of subjects across all sites?

3. * Provide justification for the sample size by explaining how you arrived at the expected number of participants and why this number is adequate for answering the research questions:

136 completers (68 cigarette smokers and 68 ECIG users) are required to achieve sufficient sample size. In order to obtain 136 completers, we may consent up to 300 individuals.

To determine sample size, we needed first to estimate effect sizes for key outcomes of subjective effect, puff topography, and plasma nicotine. Results revealed that for all within-subject analyses, 32 participants were required to achieve power >80% given a Type I error rate of 0.05. For between-subject analyses, 42 participants/group were required for plasma nicotine, 66 participants/group were required for puff duration, and 68 participants/group were required for subjective measures. Each outcome is important; thus, we are proposing 68 participants for each group in order to power for between-subject subjective effect differences at >80%, with the understanding that we may be over-powered for some measures.

4. * List the study inclusion criteria:

Individuals must be 21-55, willing to provide informed consent, attend the lab sessions and abstain from tobacco/nicotine as required. They also must be able to provide a 'positive' (cassette) cotinine results at screening.

All participants must be healthy (determined by self-report), between the ages of 21-55, willing to provide informed consent, and attend the lab and abstain from tobacco/nicotine as required. Participants must agree to use designated products according to study protocol.

Cigarette Smokers: Must use ≥ 10 cigarettes per day and have not used an ECIG in the past 30 days and who have never used an ECIG daily for one week. Cigarette smokers must have a CO level at screening of at least 15 ppm and a 'positive' cotinine cassette result to verify nicotine use.

E-Cigarette Users: Must use ECIG ≥ 3 months, ≥ 1 ml of liquid per day or approximately one cartridge or one pod, at a nicotine concentration of ≥ 3 mg/ml and have not used tobacco cigarettes in the past 30 days. E-cigarette users must also have a 'positive' cotinine cassette results to verify nicotine use.

Please note that beginning July 1, 2020, per HB1570, we will recruit individuals aged 18-55. This law "Provides an exception to the law prohibiting possession of tobacco products, nicotine vapor products, or alternative nicotine products by a person less than 21 years of age when such possession is part of a scientific study being conducted by an organization for the purpose of medical research to further efforts in cigarette and tobacco use prevention and cessation and tobacco product regulation, provided that such medical research has been approved by an institutional review board pursuant to applicable federal regulations or by a research review committee." We will not enroll anyone aged 18 - 20 until on or after July 1, 2020.

5. * List the study exclusion criteria:

Individuals with the following self-reported current, diagnosed medical condition(s) will be excluded automatically: heart-related conditions (e.g., recent heart attack/stroke, coronary heart disease), severe immune system disorders (e.g., HIV/AIDS, multiple sclerosis), respiratory disorders (e.g., COPD, asthma), kidney diseases, liver diseases (e.g., cirrhosis), or seizures.

Individuals with other self-reported current, diagnosed medical conditions (e.g., diabetes, thyroid disease, lyme disease) will be considered for exclusion after consultation with the PI and medical monitor. Participants with any medical condition/medication that may affect participant safety, study outcomes, or biomarker data will be excluded based on these consultations.

Participants with self-reported current, diagnosed psychiatric conditions or who report current psychiatric treatment or psychotropic medication use will be excluded.

Individuals with past month use of cocaine, opioids, benzodiazepines, and methamphetamine. Individuals who report using marijuana greater than 15 days in the past 30 and/or alcohol greater than 25 days in the past 30 days will be excluded. Participants who choose not to answer question related to inclusion/exclusion criteria will be excluded.

Women will be excluded if they are breast-feeding or test positive for pregnancy (by urinalysis) at screening.

Participants who weigh less than 110 pounds will also be excluded. Those who intend to quit tobacco/nicotine use in the next 30 days will be excluded and referred to cessation treatment. Individuals who report using any other tobacco products (other than what is permitted per the inclusion criteria) on a weekly or more frequent basis will be excluded.

In addition, participants who have previously participated in a study with exactly the same manipulations of ECIG type, setting, and liquid concentration will be excluded. Specifically, participants who have participated in HM20012696 will not be eligible to participate in this protocol. Staff from this protocol will work with staff from HM20012696 (who are also listed on this protocol) to assure that there is no cross-participation between participants.

6. * Will individuals with limited English proficiency be included in or excluded from this research?

- Included
- Excluded - safety concerns if participants are unable to communicate with the study team
- Excluded - instruments/measures only validated in English
- Excluded - no prospect of direct benefit to individual participants
- Excluded - minimal risk study

Study Procedures

1. * Describe the study hypothesis and/or research questions. Use lay language whenever possible.

The purpose of this study is to determine differences in nicotine delivery, use behavior (puff topography), carbon monoxide delivery, subjective effects, and physiological effects, when cigarette smokers and experienced electronic cigarette users use an electronic cigarette with different settings (different voltage and resistance settings, which together determine power levels) and different e-liquid concentrations.

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This aim involves manipulating liquid nicotine concentration and device power, testing the hypothesis that abstinence suppression, liquid consumption, and nicotine delivery will be lower as nicotine concentration is lowered, but these effects will be offset by higher power. Also, relative to smokers, ECIG users will take longer puffs, thus increasing nicotine delivery and liquid consumed.

3. * Choose all types of recruitment materials that may be used and upload them below:

- E-mail invitations
- Phone Solicitation scripts (i.e. cold calls or random-digit-dialing)
- Flyers, Mailed Letters or Newspaper/TV/Radio Ads**
- TelegRAM announcements
- Website text**
- Study-specific web sites (provide the design and text)
- Social Media
- Psychology Research Participant Pool (SONA) study descriptions
- Scripts for announcements made to groups
- Other recruitment material
- No recruitment materials

4. * Describe the study procedures/methods for identifying and recruiting participants. Address the following three aspects of recruitment in your response.

1. Identification of potentially eligible participants or secondary data/specimens of interest.

- What database(s) will be queried to identify secondary data/specimens
- How potential participants' contact information will be obtained

2. Recruitment procedures to invite participation in the study (when applicable):

- How each of the written or verbal recruitment materials and reminders (selected above) will be used
- Who will contact or respond to potential participants
- Locations where recruitment procedures will take place
- The timing and frequency of recruitment attempts

3. Eligibility screening prior to consent and how those activities will be carried out (when applicable)

See the help text for additional guidance.

Participants will be recruited via word-of-mouth and advertisements that will be posted as flyers around the community, in newspapers, on Craigslist, and possibly on social media sites such as Facebook and/or Twitter. Any postings on internet sites will use exactly the same information that is presented in those previously approved flyers (we will use advertisements that are already approved as part of the CBPL/CSTP registry: HM20002567; there is not a study-specific flyer for this study). Potential participants will make the initial contact via telephone by calling the phone number provided on the advertisements, or by going to the website provided on the advertisements. Please note that for the initial screening, we will use a multi-study screening process/registry described in HM 20002567. Participants who appear eligible based on the initial screening questionnaire (in HM20002567 and attached) are then contacted (either via phone or e-mail), told about this study using only language from the approved consent form (via phone), and if interested, participants are invited for an in-person screening, where consent for this study will be obtained.

Individuals who are participants in other, ongoing CBPL/CSTP studies (participants with whom we have a pre-existing relationship) may be verbally referred to this study, and directed to either call the laboratory or visit the website indicated on the advertisements/flyers, if they are interested.

Participants who are eligible and who choose to enroll may be contacted via text for appointment reminders if they agree (see scripts).

5. * Does this study have a separate protocol document (i.e. a multisite or sponsor's protocol) that contains a detailed description of the study's methodology?

- Yes
- No**

6. * Since a separate protocol document is not uploaded, describe the proposed research using language understandable to those IRB committee members whose expertise is not scientific. The description must include:

- 1. A statement explaining the study design**
- 2. A detailed description of all the procedures that will be followed to carry out the study, preferably in**

sequential order, and in sufficient detail that the study's methods could be replicated
3. A description of all research measures/tests/interventions that will be used (if applicable)

See the help text for additional guidance

Participants will first be screened via phone or online, via a multi-study screening process/registry described in HM 20002567 (see attachment "Registry consent form and questions"). Participants can tell study staff if they are interested in screening for a particular study only. All screening data collected from participants who choose to join the registry will be used in this study. Participants who appear eligible will then be scheduled for an in-person screening visit (the in-person screening visit is part of this protocol, not part of the registry process) where they will provide informed consent if they choose to participate and complete other forms (see in-person screening forms: ICF, Health Information Form, Biochemical test/vitals form, Penn State Cigarette Dependence Index, PROMIS or PROMIS-E, and FTND. These will be completed via RedCap). Age will be verified by asking participants to provide some form of identification that include a date of birth. If participants are very clearly over age 30, we may not check ID. Participants will also be able to view other questionnaires (Direct Effects of Vaping Questionnaire, Direct Effects of Nicotine Questionnaire, Hughes-Hatsukami Questionnaire, and the General Labeled Magnitude Scale), via computer, and the study equipment. Last, we will take pictures of participants e-cigarette devices and liquids so that we can better describe what they are using.

After screening and informed consent, eligible participants will enroll in this study, which is modeled on our previous work (e.g., Spindle et al., 2016; Hilier et al., 2017). A total of 136 participants (68 cigarette smokers and 68 experienced ECIG users) are needed to complete the study. Once enrolled, participants will attend the lab for six additional experimental sessions (approximately 4 hours each) where they use an "open system" ECIG (Kanger Sub Box Mini) set to either 15 watts or 30 watts, which will contain either 10mg, 15 mg, or 30 mg nicotine-containing liquid. The design of this study is within-subjects, thus, all participants will complete six sessions that differ by the combination of watts and liquid concentration. Sessions will be ordered by Latin-square. The sessions will occur no more than 2 days per week and will be separated by at least 48 hours. The approximate total time that participants will be in the laboratory is 24.5 hours (30 minutes for screening and 24 hours for sessions). This does not include the 12 hours before each session that we ask participants to abstain from and nicotine/tobacco containing products.

During each session, participants will first complete a 10-puff product use bout, and then a 90-minute ad lib product use bout. Sessions will be preceded by 12 hours tobacco/nicotine abstinence (to measure the extent to which each device/liquid combination suppresses nicotine/tobacco abstinence symptoms), and session order will be ordered by Latin-square. In all sessions, participants will use topography-measurement equipment (a mouthpiece attached to the ECIG that is attached to a computer via tubing; the participant then puffs on the mouthpiece). Other outcomes include plasma nicotine, cardiovascular response, carbon monoxide level, and subjective effects (direct effects of the ECIG and nicotine, abstinence symptoms).

More specifically, upon arrival at the laboratory for each session, participants' breath CO will be measured to ensure compliance with the overnight abstinence criteria (i.e. CO < or equal to 10 ppm for cigarette smokers, see Breland et al., 2006, or < or equal to 7 ppm for ECIG users). In addition, participants will be asked questions about symptoms experienced since the last visit. Once deemed abstinent, participants will begin a 1-hour waiting period. During this time, participants cannot eat or use their cell phones, although water, movies, and/or magazines will be provided. We have recently instituted this 1-hour waiting period in other studies, because we find, after looking at plasma nicotine levels which are analyzed months after participants complete studies, that some participants do not comply with the 12-hour nicotine/tobacco abstinence requirement. Adding this 1-hour waiting period ensures that all participants are abstinent for at least one hour before the session begins. After the 1-hour waiting period, an IV catheter will be inserted into a forearm vein of the participant, physiological monitoring equipment will be attached (arm blood pressure cuff, pulse oximotor placed on finger), and a 30-minute rest period will begin. This rest period allows us to measure resting heart rate and blood pressure immediately before product administration. A detailed timeline of the sessions is described below. Please note that because catheter insertion can be difficult, we will attempt to insert a catheter no more than three times in one day, and if all three attempts are unsuccessful, the session will be discontinued, with payment as outlined in the consent and compensation section.

The subjective questionnaires administered at each time point are as follows: Direct Effects of Vaping Questionnaire, Direct Effects of Nicotine Questionnaire, Hughes-Hatsukami Questionnaire, and the General Labeled Magnitude Scale. All of these questionnaires will be administered via computer or RedCap with the exception of the General Labeled Magnitude Scale, which may be administered via paper and pen, or via RedCap. At the end of each session, participants will also be asked one additional question: "Do you believe that you received nicotine today?" (Participants' answer will be entered into RedCap).

Experimental session timeline (times approximate):

Participant arrives, CO test to confirm tobacco abstinence, additional questions about symptoms asked
0 Hr 00 1-hour waiting period
1 Hr 00 Hr Insert venous catheter, attach physio equipment, 30-minute rest period begins
1 Hr 30 Subjective effects questionnaires, baseline blood sample 1, CO test
1 Hr 35 10 puffs from ECIG (30s inter-puff interval)
1 Hr 40 Blood sample 2 (immediately after last puff), subjective effects questionnaires, CO test
2 Hr 00 Blood sample 3, subjective effects questionnaires, CO test, ad lib use period begins
3 Hr 30 Ad lib use period ends, blood sample 4, subjective effects questionnaires, CO test
Participant asked last question, "Do you believe that you received nicotine today?"
Remove Catheter
Stop Physio Monitoring
Payment
Release

7. * The IRB only reviews research activities, so indicate which of the study activities are:

- Being performed exclusively for research purposes (i.e. they would not otherwise be done apart from this study) VERSUS.
 - Alterations of routine activities/procedures (e.g. the study is altering the timing, frequency, method, location, amount, etc.) VERSUS.
 - Being done for other purposes and whose data/results will be used secondarily in the study (e.g. standard medical or psychological tests, routine education practices, quality improvement initiatives, etc.).
- All procedures are performed exclusively for research purposes.

8. If applicable, describe alternatives (research or non-research) that are available to potential participants if they choose not to participate in this study:

9. Upload any supporting tables or documents (e.g. protocol documents, figures/tables, data collection forms, study communications/reminders):

Upload ALL instruments/guides that will be used or that participants will experience (i.e. see, hear, complete), including measures, scripts/questions to guide interviews, surveys, questionnaires, observational guides, etc.:

Upload ALL recruitment and screening materials, including such as ads, flyers, telephone or in-person scripts, letters, email invitations, TelegRAM announcements, and postcard reminders, screening scripts, screening forms, and screening measures:

Behavioral Intervention Details

1. * Describe the duration of the social/behavioral intervention, task, or environmental manipulation:

Six sessions that are about 4 hours long each.

2. * Describe any potential harms or discomforts that participants could experience during the intervention:

From the consent form:

1. You may experience some discomfort during abstinence from cigarettes and nicotine before the session or while using electronic cigarettes during the session. Side effects from products that contain nicotine can include sweating, lightheadedness, dizziness, nausea, and nervousness. These effects are less likely in individuals who use nicotine-containing products regularly. In addition, some people who use e-cigarettes experience seizures.
 2. The e-cigarette liquid that we give you may contain more nicotine than you usually use, although some e-cigarette users report using these liquids. Inform the study staff immediately if you experience any discomfort.
 3. On very rare occasions, you may experience small droplets of liquid during inhalation of the electronic cigarette we provide. You may find these droplets to be unexpected and/or unpleasant. This experience has been reported by electronic cigarette users, and they report that it is an annoyance that does not appear to present any medical danger. If this occurs, we will immediately replace the electronic cigarette device you are using.
 4. Side effects from tobacco/nicotine abstinence can include irritability, anxiety and restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. These are common abstinence symptoms in cigarette smokers. Though uncomfortable, these feelings are not medically dangerous.
 5. You may also feel some discomfort when the nurse inserts or withdraws the needle, or when blood samples are taken. We try very hard to minimize your discomfort at these times, and the use of a trained nurse and sterile, disposable equipment enhances comfort while reducing the risk of bruising and infection.
 6. Your heart rate and blood pressure may increase; if either increases above acceptable limits, your participation may be stopped for your safety.
 7. You may find the monitoring equipment uncomfortable.
 8. The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in the study.
 9. The use of e-cigarettes involves risks that are currently unknown or unforeseeable. Using e-cigarettes may involve risks to a developing embryo or fetus that are currently unknown.
- Non-Physical Risks:
10. Participation in research might involve some loss of privacy. There is a small risk that someone outside the study could see and misuse information about you.
 11. The study questionnaires ask personal questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable.

3. * Will the intervention be physically invasive or painful?

Yes

No

4. * Describe the impact the intervention will have on participants, including the nature and duration of any impact(s):

Participants will be using an ECIG that contains nicotine, so they may experience the effects of ECIG use which could include sweating, lightheadedness, dizziness, nausea, and nervousness, although these are less likely in individuals who use nicotine-containing products regularly. All of the participants are experienced ECIG users or cigarette smokers. The duration of these impacts is the length of the session.

5. * In the investigator's opinion, is there any reason to think that the participants will find the intervention offensive or embarrassing? Explain why or why not.

No.

Sample Collection Details

1. * Select all of the types of samples that will be collected as part of this study.

- Amniotic Fluid
- Blood**
- Buccal Smears
- Saliva
- Tissue
- Urine**
- Other**
- None of the Above

2. * If Other, please describe the type of sample being collected:

Breath for carbon monoxide sample.

3. * Select all of the methods of blood collection that will be utilized in this study:

- Individual Needle Stick(s)
- Indwelling Catheter Placed Solely for This Study**
- Indwelling Catheter Placed for Other Reason(s)
- Blood Collected at the Same Time as Non-Research Blood Collection(s)
- Other

4. * In order to collect urine, will an indwelling catheter be placed solely for the research study:

- Yes
- No**

5. * Describe how the sample will be collected and the collection schedule. For each type of sample, include information about

- The procedures that will be followed to collect the sample
- The role(s) of the individuals who will collect the sample
- The volume/size range of the sample
- The timing and frequency of sample collection

Urine will be collected at the in-person screening for this protocol to test for cotinine & pregnancy (pregnancy testing for women only). Urine will not be stored for later use.

Upon arrival at the CBPL for the research session, participants' breath CO will be measured to ensure compliance with the overnight abstinence criteria (i.e. CO less than or equal to 10 ppm for cigarette smokers and less than or equal to 7 ppm for experienced ECIG users).

Blood will be collected via intravenous catheter 4 times at each session (7 ml each time), for a total of 24 samples per person in the entire study (168 ml in total). Blood not be collected more than 2 times per week.

6. * Will genetic testing or analyses be conducted on any of the samples:

- Yes
- No**



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ID: HM20012738

View: SF2 - Active Internet Data Collection

HM20012738 - Alison Breland

Effects of Electronic Cigarette Settings and Liquid Concentrations in Cigarette Smokers and Electronic Cigarette Users

Active Internet Data Collection

1. * Describe the platform/technology chosen for collecting the data and transmitting data securely over the internet. Give the rationale for selecting this technology.

The in-person screening questionnaires and questionnaires administered during sessions will be administered via RedCap. All of the data will be stored in REDCap, and viewing will be restricted to those personnel associated with this protocol (listed under personnel).

2. * Describe how data will be linked or unlinked to identifiers including email addresses, names, and/or IP address.

Data will be linked to participant IDs and dates of birth.

3. * Is there an alternative method for completion of the data collection other than the internet?

Yes

No

4. * If yes, describe the alternative(s).

Paper forms.

5. * Describe how individuals will be able to skip or not answer particular questions. If any questions are mandatory, provide justification.

Participants do not have to answer any particular question that they do not want to answer. If a participant does not want to answer a question, he/she can inform study staff and study staff, who can note this and remove answers (some of our questionnaires do not have an option to skip the question because it is difficult to add this option in RedCap without making the forms confusing, and also, if we make all the questions in RedCap optional, we find that this leads to participants missing questions by mistake).

6. If not including children, describe any procedures used to verify that research participants are adults.

We ask participants for their age and date of birth several times (telephone or online screening, in-person screening) and verify that the answers are the same.



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View: SF2 - Secondary Data/Specimen Details

HM20012738 - Alison Breland

Effects of Electronic Cigarette Settings and Liquid Concentrations in Cigarette Smokers and Electronic Cigarette Users

Secondary Data/Specimen Details

1. * Describe the source(s) and nature of the information/specimens being obtained. This response should:

- Identify where the data/specimens will come from (e.g., another researcher's registry, pathology lab, commercial source, medical records, etc.); and
- List what types of specimens will be obtained (when applicable); and/or
- List all data elements that will be obtained (when applicable). A data collection form or other documentation may be uploaded and referenced here.

Contact information and eligibility requirements are obtained from this registry. Eligibility questions include information about cigarette and electronic cigarette use, alcohol and drug use, health issues and medication use. This data is used for screening and eligibility purposes. Please note that we may take data collected in the registry and add it to data collected in this usage protocol (ONLY for individuals who have signed consent forms for this usage protocol).

2. * Describe whether any agreement exists between you and data/specimen provider that states you will never have access to the ability to identify the participants (i.e. access to identifiers or the code key) and that you will not attempt to re-identify individuals.

The registry contains identifying information such as names. If a participant enrolls in this study, they are given an alphanumeric code that is connected to their registry information, via a separate variable in our administrative forms. This electronic key can be deleted once the usage protocol is complete. The purpose of this link between the registry and this usage protocol is to help us keep track of which participants are participating in which usage protocol.

We can re-identify participants.

3. * When the information/specimens were originally collected, did individuals provide consent for secondary research use of their data/specimens (i.e. consent to another research study or to a research registry)?

- Yes
 No

4. * Provide name(s) of the registry/repository being accessed.

CSTP Overall Screening and Registry

5. * Site having responsibility for the management of this registry/repository:

- VCU
 Non-VCU

6. If the registry / repository is located at VCU, provide the IRB number for the registry / repository.

HM20002567

7. * Is the original consent form that participants signed upon entry into the registry / repository available?

- Yes
 No

8. If YES, the original consent is available, upload it for the IRB to reference

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ID: HM20012738

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View: SF2 - Costs to Participants

HM20012738 - Alison Breland

Effects of Electronic Cigarette Settings and Liquid Concentrations in Cigarette Smokers and Electronic Cigarette Users

Costs to Participants

1. * Select all categories of costs that participants or their insurance companies will be responsible for:

- Participants will have no costs associated with this study
- Study related procedures that would be done under standard of care
- Study related procedures not associated with standard of care
- Administration of drugs / devices
- Study drugs or devices
- Other

Compensation

1. * Describe any compensation that will be provided including:

1. total monetary amount
2. type (e.g., gift card, cash, check, merchandise, drawing, extra class credit)
3. how it will be disbursed

Participants will be paid \$10 after the in-person screening visit. Participants will receive \$50 after completing the first session, \$75 after completing the second session, \$100 after completing the third, fourth sessions, \$150 after completing the fifth session, and \$175 after completing the sixth session. Thus, the total amount participants could earn for the entire study is \$660. If a participant chooses to leave the study early, he or she will keep the amount earned up to that point. In addition, if a session must be discontinued for reasons beyond the control of the participant, the participant will be paid for the time spent complying with study conditions before the session began (\$15) and also the time spent in the laboratory (\$15/hour). All payments will be in the form of cash.

This amount was chosen because of the number of hours that participants are asked to be in the laboratory (24 hours for sessions), which does not include the 12 hours that we ask them to abstain from tobacco products before they come to the lab for each session. In addition, we will insert an in-dwelling catheter for each session. With the time involved in the laboratory, time abstaining before coming to the laboratory (which can be very unpleasant) and possible discomfort from the catheter, we feel that the compensation is appropriate, and not coercive--in order to receive payment, participants have to do quite a bit.

In addition, there may be rare instances in which the equipment we use malfunctions during a session. If this happens, we may stop the session and ask the participant to return on another day to repeat that session. In these instances, if the equipment malfunctions in the first half of the session, we will pay participants half of the money they would have earned in that session. If the equipment malfunction occurs in the second half of the session, we will pay the participant the full amount for that session.

2. If compensation will be pro-rated, explain the payment schedule.

3. * Will Social Security Numbers be collected for compensation purposes only?

- Yes
- No

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View: SF2 - Consent Process

HM20012738 - Alison Breland
 Effects of Electronic Cigarette Settings and Liquid Concentrations in Cigarette Smokers and Electronic Cigarette Users

Consent Process

1. * List all consent groups:

Group	Types	Waivers	Roles	Roles - Other	Consent	Coercion	Decision	Re-Consent
View All participants	Signed Consent by Participant	No Waivers Requested	Research Nurse Research Assistant Trainee/Student(working on project)		Consent for this study will be obtained in the in-person screening visit. Consent will be ongoing and assumed when a participant makes and completes follow up appointments. Lab staff will call the participants the day before their scheduled appointment and remind participants about upcoming appointments, go over study procedures, and check to make they are still interested in participating. This will occur before each appointment in which consent is assumed when participants show up for a session.	The research study will be described fully to participants, and they will be allowed to ask as many questions as they would like. At any point participants can choose to not continue with the various levels of screening for this study (the online/telephone consent/screening and in-person consent/screening).	Participants will be given as much time as needed to consider the research study and consent form before deciding whether or not to participate.	

2. Upload any consent / assent documents:

Consent Groups

1. * Enter a descriptive name for this consent / assent group:

All participants

2. * Select all that apply to this consent / assent group:

Name

- Signed Consent by Participant
- Signed Parent/Guardian Permission or Legally Authorized Representative Consent
- Signed Assent by Child or Decisionally Impaired Adult
- Verbal Assent by Child or Decisionally Impaired Adult
- Short Form Consent (limited applicability)
- None of the Above (select waiver below)

3. * Select any waivers that apply to this consent / assent group:

- No Waivers Requested
- Waiver of All Consent or Some Elements in Consent Form
- Waiver of Parental Permission or Legally Authorized Representative Consent
- Waiver of All Assent by Child or Decisionally Impaired Adult
- Waiver of Signature on Consent/Permission Forms (waiver of documentation of consent)
- Exception from Informed Consent (for emergency research only)

4. * Select all study team role(s) that will obtain consent / assent from this group:

- Principal Investigator
- Co/Sub-Investigator
- Medical or Psychological Responsible Investigator
- Lead Student/Trainee Investigator (leading their own project)
- Research Coordinator
- Research Nurse
- Consultant
- Research Assistant
- Pharmacist
- Statistician
- Regulatory Coordinator
- Trainee/Student(working on project)
- Other
- N/A: Requesting Waiver of Consent

5. * Describe the consent procedures used for this group. Include when, where, and how consent / assent will be obtained both initially and, if applicable, during ongoing participation in the study:

Consent for this study will be obtained in the CBPL, at the in-person screening visit. Consent will be ongoing and assumed when a participant makes and completes follow up appointments. Lab staff will call the participants the day before their scheduled appointment and remind participants about upcoming appointments, go over study procedures, and check to make they are still interested in participating. This will occur before each appointment in which consent is assumed when participants show up for a session.

6. * Describe the process for minimizing any potential perception of undue influence to participate when there is a pre-existing relationship between the participant and the researcher (e.g. treatment provider/patient; instructor/student; supervisor/employee, etc.):

The research study will be described fully to participants, and they will be allowed to ask as many questions as they

would like. At any point participants can choose to not continue with the various levels of screening for this study (the online/telephone consent/screening and in-person consent/screening).

7. * How much time will participants be given to make a decision:

Participants will be given as much time as needed to consider the research study and consent form before deciding whether or not to participate.

8. If applicable, describe the procedures for consenting children upon entering adulthood or participants who are no longer decisionally impaired:

Risks, Discomforts, Potential Harms and Monitoring

1. * Describe the risks of each research procedure to participants or others. For each identified risk, provide an assessment of the anticipated seriousness and likelihood of the risk. Some examples of possible risks include but are not limited to:

- Physical risks (e.g. bodily harms or discomforts, side effects, etc.)
- Psychological risks (e.g. emotional, mental, or spiritual harms or discomforts, changes to thoughts, beliefs, or behaviors, etc.)
- Research data risks (e.g. loss of confidentiality and privacy)
- Social or legal risks (e.g. impacts on relationships or reputation, legal or criminal justice actions for self or others, etc.)
- Financial risks (e.g. impacts on income, employability, or insurability, loss of services, etc.)
- Other risks (e.g. unforeseeable risks of experimental procedures, risks related to particular study designs (randomization, washout, placebo, withholding care/services, deception), etc.)

See the help text for additional guidance.

This protocol uses established methods and procedures and involves only minimal risk to participants. Twelve hours of tobacco/nicotine abstinence may cause mild discomfort and nicotine abstinence symptoms. Nicotine abstinence symptoms are not medically dangerous but participants may experience include: irritability, anxiety and restlessness, excessive hunger, difficulty concentrating, and sleep disturbance. The risks of using ECIGs/nicotine are routine for the target population. Risks of nicotine use include sweating, lightheadedness, dizziness, nausea, and nervousness. These effects are unlikely in individuals who use tobacco products regularly. In addition, some people who use e-cigarettes have experienced seizures (<https://www.fda.gov/tobacco-products/ctp-newsroom/some-e-cigarette-users-are-having-seizures-most-reports-involving-youth-and-young-adults>). These have been reported among individuals with a history of seizures as well as among individuals using other substances such as marijuana and amphetamines, as well as among others. In addition, recently there have been some cases of e-cigarette use being associated with respiratory illnesses such as difficulties breathing, cough, shortness of breath and/or chest pain before hospitalization. In some cases, e-cigarette use has led to death, although most of these cases have been related to vaping THC. In some cases symptoms of mild to moderate gastrointestinal illness such as nausea, abdominal pain, vomiting, diarrhea, or fevers or fatigue have been reported. The Centers for Disease Control and Prevention advises that e-cigarette, or vaping products are unsafe for youths, young adults, or women who are pregnant, although e-cigarette use is most common in this country among 18-24 year-olds.

Adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products. Last, blood sampling involves the minor risk of infection and bruising at the catheter site.

We have read that users of the ECIG device we are using in this study sometimes experience small drops of liquid during inhalation, and we have occasionally noticed this during our testing of the product. If this occurs, participants may find the droplets unexpected and/or unpleasant. We believe that is unlikely that these small droplets of liquid present any medical danger. Currently, there is no known or confirmed risk to the droplets that we are aware of.

It is unlikely that the questionnaires will pose any potential risk or discomfort (no sensitive questions are being asked). Sessions are relatively short, and we find that participants tolerate 4-hour sessions well (i.e., they do not become fatigued).

There is a small risk of loss of confidentiality, discomfort with monitoring procedures, and increased heart rate/blood pressure.

There is little available data on the range of power settings (in Watts) and liquid concentrations that ECIG users use. One paper described data on power and liquid settings for 165 adult users in California, which showed a median power setting of 204.5 W, although the authors note that many participants were not able to accurately report their power settings. In the same study, the median liquid concentration was 6.0 mg/ml nicotine with a range of 0 - 30.0 mg/ml. Data collected in an ongoing study in the CBPL/CSTP for N = 44 shows an average power setting of 55.3 W (range = 6.8 - 204 W) and a mean liquid concentration of 7.6 mg/ml nicotine (range = 3 - 18 mg/ml). We have conducted a variety of ECIG studies previously in the CBPL/CSTP with liquid that is 36 mg/ml nicotine. Finally, information from e-cigarette forums indicates that individuals are using both low and high nicotine liquids (35 - 50 mg/ml, for example) in "third generation", variable-wattage devices like the one we are proposing to use in this study. We are not aware of specific risks associated with different liquid/power settings other than what ECIG users are exposed to with use in general.

2. * Describe how each of the risks/harms/discomforts identified above will be minimized:

Participant safety and rights will be protected by highly trained staff that is well-versed in the importance of maintaining confidentiality. Participants will be informed of the potential symptoms of nicotine abstinence/withdrawal, and will be told that they are free to leave the study at any time. Risk of infection from blood sampling is minimized by trained nursing staff, disposable equipment, and aseptic nursing procedures. In the 15 plus years of operation, the CSTP has completed numerous IRB-approved studies without participant injury or a breach of confidentiality.

In addition, non-invasive computerized monitoring equipment allows for minute-by-minute, real time monitoring of participants' heart rate and blood pressure (BP). Research personnel are trained to alert the research nurse if heart rate exceeds 120 beats per minute, if systolic BP exceeds 150 mm Hg, or if diastolic BP exceeds 100 mm Hg. Individuals whose heart rate and/or BP levels remain elevated will be monitored continually by the nurse, and if necessary emergency responders will be notified. Emergency medical coverage is available via the emergency room that is a half block away from the CBPL.

In the case of nicotine abstinence symptoms, the project products will possibly alleviate these risks. Participants will be provided with water at all times.

The risk of seizures is minimized by excluding participants with any history of seizures, and by having a full-time RN available, as well as monitoring of vital signs. In addition, some of the reported seizures occurred in users who were using other substances such as marijuana or amphetamines—the risk of seizures in this study is reduced as we are administering nicotine and no other substances.

The risk of respiratory illnesses related to ECIG use is minimized by the limited ECIG use that occurs in each session

(10 puffs plus a 90 minute ad lib use period). Participants are informed about recent reports of ECIG-related respiratory illnesses, and that most of the cases have been related to vaping THC. Participants are also informed that the Centers for Disease Control and Prevention advises that e-cigarette, or vaping products are unsafe for use by youths, young adults, or women who are pregnant and that adults who do not currently use tobacco products should not start using e-cigarette, or vaping, products. Participants are also advised to monitor themselves for symptoms and to seek medical attention if they have concerns. In addition, we will ask about respiratory and gastrointestinal symptoms at screening and before each session begins. Answers given at the beginning of each session will be compared to the participants' previous answers, and if any symptoms have increased, Dr. Lipato will be asked to review the symptoms. In some cases, we may contact Dr. Lipato to determine if a session can proceed.

Please note that for this study we will recruit cigarette smokers and ECIG users who are aged 18 or older but consider recruitment of individuals 18 -25 as minimal risk, as the definition of "minimal risk" includes: "...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." Our inclusion criteria make clear that participants in this study are exposed to nicotine in their daily life, thus the risk of this exposure are, by definition, minimal.

We recruit individuals aged 18 + who use nicotine-containing products at similar or higher daily/weekly frequencies that they would be exposed in the laboratory setting. For example, our exclusive e-cigarette users must report ingesting >=1 ml of e-cigarette liquid/day or approximately one pod/cartomizer per day of at least 3 mg/ml nicotine for the past 3 months or longer. Our cigarette smokers must report smoking at least 10 cigarettes per day, have a CO level at screening of at least 15 ppm (indicates recent smoked tobacco use). In addition, all participants must have a positive cotinine test at screening, to verify recent nicotine use. Thus, our protocol ensures that any study-related nicotine/tobacco exposure is not greater than that to which participants expose themselves as part of their ordinary life.

During the sessions, if the participant experiences small droplets of liquid during inhalation, we will immediately replace the device he or she is using in the session.

Participants will be able to view all questionnaires used in sessions before attending sessions, and will be informed of the length of each session. If participants do not want to answer the questionnaires, or feel that the length of the sessions will be too long, they can choose to not participate.

Finally, as a precaution, we have added to the consent form that the e-cigarette liquids we give to participants may contain more nicotine than they are used to, although some e-cigarette users report using these concentrations. Participants are instructed to inform research staff if they experience any discomfort.

3. * Describe any potential risks or harms to a community or a specific population based on study findings (e.g. information that could be stigmatizing or derogatory):
None.

4. Where appropriate, discuss provisions for ensuring necessary medical, professional, or psychological intervention in the event of adverse events to the subjects:

Individuals whose heart rate and/or BP levels remain elevated will be monitored continually by the nurse and if, necessary, emergency responders will be notified. Emergency medical converge will be available via the emergency room that is 1.5 miles from the CBPL/CSTP.

5. * Describe criteria for when the investigator would withdraw an individual participant from the study; such as safety or toxicity concerns, emotional distress, inability to comply with the protocol, etc.:

Participants may be withdrawn from the study if the PI or study nurse has any safety concerns (such as continuous high blood pressure or heart rate) during sessions, or if an intravenous catheter cannot be successfully inserted.

Additionally, participants can be withdrawn if they are unable to follow protocol guidelines and/or are unable to keep their scheduled session appointments.

6. * Summarize any pre-specified criteria that would trigger the investigator/sponsor/monitoring committee to stop or change the study protocol due to safety concerns:

At this time we do not have a pre-specified criteria for stopping or changing the study protocol due to safety concerns.

Data and Safety Monitoring

Data and safety monitoring is a system for checking the study's data at regular intervals over the study period to identify and address issues that could affect the safety of research participants. This requirement is in accordance with 45 CFR 46.111.

The purpose of data and safety monitoring plan is to set forth study team procedures for monitoring/addressing:

- Participant safety (physical, psychological, etc.)
- Data validity
- Early stopping (termination) based upon changes in risks and benefits.

7. * Indicate if this study will have a Data Safety Monitoring Board (DSMB) or a Data Safety Monitoring Plan (DSMP): [Required for all greater than minimal risk studies]

DSMB

DSMP

No DSMB/DSMP [Note: This response is not applicable for greater than minimal risk studies]

Privacy

Privacy refers to an individual's right to control how others view, record, or obtain information about them. When privacy is violated it can involve such things as

- Being asked personal questions in a public setting;
- Being publicly identified as having a particular characteristic or diagnosis;
- Being seen entering a place that might be stigmatizing;
- Being photographed, videotaped or observed without consent;
- Disclosure of personal information to unauthorized people

Privacy is not the same as confidentiality because privacy protections apply to people, and confidentiality protections apply to data. Confidentiality protections should be described on the Data Confidentiality page of this form, not here.

Instructions for this page:

Select all the applicable ways that the research team will protect participants' privacy throughout the course of the study. Not all will be applicable to every study.

To elaborate on any response, also click the "Other Protections" checkbox to provide further explanation in the last free-text question.

Read the entire page before filling out the form.

1. * Protections when conducting one-on-one in-person interventions or interactions (for groups see Q2 below):

- Conducting study activities in locations that maximize privacy (limited people around, closing doors, drawing drapes around beds, monitoring voice volume, etc.)
- Verifying identity before discussing personal information.
- Asking the participant if they are comfortable answering questions in that location
- Asking the participant if they are comfortable with having other people present (if any)
- Moving away from other people when conducting activities in public spaces or offering a private space
- Offering other options of ways to respond to sensitive questions (i.e. pointing, clicking, or writing) if uncomfortable verbally responding
- Using generic signs on research rooms and spaces, particularly for research on stigmatizing or sensitive topics
- Other protections not listed in this question – describe below
- N/A – study has no in-person interventions or interactions with participants

2. * Protections when conducting group interventions or interactions:

- Conducting study activities in locations that maximize privacy (limited people passing by, closing doors, monitoring voice volume, etc.)
- Moving to a more private area to answer questions or to discuss concerns
- Discussing privacy with the participants and the importance of not talking outside the group about what other people say during the group session
- Allowing participants to use a pseudonym or limiting use of individuals' names during the group activity
- Asking everyone in a public group setting (e.g. classrooms, workshops) to turn something in (blank or filled) so participants do not have to self-identify when turning in materials
- Collecting paper forms in a closed box or envelope rather than passing to others or leaving in an open area
- Limiting participant identifiers that would be visible on paper documents (i.e. using study IDs instead of direct identifiers)
- Allowing people to distance themselves from other participants during group activities
- Offering other options of ways to respond to sensitive questions (i.e. pointing, clicking, or writing instead of speaking)
- Using generic signs on research rooms and spaces, particularly for research on stigmatizing or sensitive topics
- Ensuring non-participating individuals are not captured on recordings or in photos
- Other protections not listed in this question – describe below
- N/A – study has no group interventions or interactions

3. * Protections when conducting remote interventions or interactions (e.g. phone, text, video-conference, tele-health, online, etc.):

- Conducting study activities in locations where study staff can maximize their own privacy (limited people around, closing doors, monitoring voice volume, etc.)
- Leaving/sending generic messages that avoid using study and participant identifiers, such as names, study titles, clinics, study topics, etc.
- Obtaining permission prior to sending text messages
- Advising the participant to move to a location where they are comfortable answering questions and will not be overheard

- Advising online participants to complete the activity at a time and location where they will be comfortable answering questions
- Ensuring non-participating individuals are not captured on recordings or in photos
- Offering other options of ways to complete the activity (i.e. online, paper, phone) if more privacy is desired
- Offering a way to save and return later to the online activity if privacy is compromised
- Other protections not listed in this question – describe below
- N/A – study has no remote interventions or interactions with participants

4. * Protections when mailing study materials to/from participants:

- Obtaining permission to mail study materials
- Confirming/verifying the accuracy of addresses before mailing items
- Ensuring the participant is able to personally receive mailed materials and has a way to protect their own privacy if they do not want others to know they are receiving research communications (i.e. notifying participants of when to expect it)
- Using return address labels and document headers that avoid study identifiers, such as study names, clinics, study topics, etc.
- Avoiding or limiting use of participant identifiers and health information on mailed documents (i.e. using study IDs instead of direct identifiers)
- Providing a return mailing address label or pre-addressed envelope to ensure returned items are sent to the correct address
- Communicating receipt of mail from participants and/or asking them to notify you when they mail it to ensure study documents are not lost in transfer
- Offering other options of ways to complete the activity (i.e. by phone or online) if desired
- Other protections not listed in this question – describe below
- N/A – not mailing any materials to/from participants

5. * Protections when analyzing or disseminating study data *Applicable to all studies*:

- Working only in locations where the study team can ensure privacy (not working in close proximity to non-study personnel, closing doors, closing/putting away documents/files before leaving, etc.)
- Securing physical materials only in locations that ensure privacy (access limited to authorized study personnel)
- Only sharing data/specimens in accordance with the Sharing Plan outlined in this smartform
- Obtaining explicit parental permission before disseminating or sharing recordings or photos of children
- Blurring/redacting/hiding faces and other identifiable features/marks (tattoos, scars, birthmarks, distinctive voice, etc.) in recordings or photos prior to disseminating or sharing
- Other protections not listed in this question – describe below

6. * If “other protections” was selected in one or more of the questions above, describe all the other way(s) that the research team will protect participants’ privacy. See the help text for additional guidance.

Participants’ privacy and comfort will be addressed throughout the course of the study. During the intake process and session, participants will be seated in a private room. All study procedures will take place behind closed doors. Participants will be informed that they may withdraw from the research study should they find any research procedures unacceptable. All participants and data will be treated with professional standards of confidentiality. Data are identified by numeric code only and stored under double lock or in RedCap. Participants’ names are not directly linked to data within this protocol, although we will add participants’ study ID from this protocol to the registry associated with this protocol, which does contain first names. Briefly, a numeric code is assigned to each participant when they provide informed consent, and the part of the numeric code relates to the order in which the individual consented. This numeric code appears on all data. Access to the key and the consent documents is restricted to study investigators and staff. these individuals perform the informed consent and conduct the study with he participants so they already know who the participants are and observe the participants as data are collected. Participants’ research related information will be withheld, consistent with the law, unless permission is given to release such information. Effectiveness is indexed by previous experience: we have used these procedures for over 15 years and have not had a single incident in which a participants’s confidential information has been compromised.

Data Confidentiality and Storage

Confidentiality refers to the way private, identifiable information about a participant or defined community is maintained and shared. It describes how the study's research materials (data, specimens, records, etc.) are protected from unauthorized access.

Instructions for this page:

Select all the ways that the research team will keep the study materials and data confidential throughout the course of the study. Not all will be applicable to every study. To elaborate on any response, also click the "Other Protections" checkbox to provide further explanation in the last free-text question.

Read the entire page before filling out the form.

1. * Protections for paper research materials:

- Maintaining control of paper documents at all times, including when at an off-campus location
- Limiting or avoiding use of participant identifiers on paper documents (i.e. using study IDs instead of direct identifiers)
- Storing paper documents in a secure location accessible only to authorized study personnel
- Promptly transcribing, scanning, or abstracting data from paper into electronic platforms with destruction of the paper copy
- Proper destruction of paper records (and obtaining prior permission when required) in accordance with VCU Records Management policies
- Other protection not listed in this question – describe below
- N/A – no paper research materials

2. * Protections for research specimens:

- Maintaining control of specimens at all times, including when at an off-campus location
- Storing specimens in a secure location accessible only to authorized study personnel
- Labeling specimens with subject ID or other coded information instead of direct identifiers
- Final destruction of specimens will be devoid of any identifiable information
- Other protection not listed in this question – describe below
- N/A – no research specimens

3. * Protections for electronic files/data - See <https://ts.vcu.edu/about-us/information-security/data-management-system/>

- *Required for all studies* Use VCU-approved methods of data storage, transmission, and transfer (see <https://dms.vcu.edu>)
- Remotely accessing VCU network storage to store data when at off-campus locations
- Ensuring unauthorized individuals who might share a device do not have access to study materials (e.g. individual logins, separate accounts)
- Using VCU-approved data collection tools and apps (i.e. REDCap, Qualtrics) and storing exported analysis files in VCU-approved storage locations (see <https://dms.vcu.edu>)
When using non-VCU-approved electronic data collection tools, storage locations, data transfer platforms, and mobile apps (e.g. Dropbox, Box, Survey Monkey, Fitbits, novel apps): • consulting with VCU Information Security on proper data management (see <https://ts.vcu.edu/askit/essential-computing/information-security/>); • advising participants about the terms of use and privacy policies of those sites/apps; • limiting or avoiding use of identifiers; and • removing data promptly from the external location after transferring it to a VCU storage location
- De-identifying the research data by replacing subjects' names with assigned subject IDs
- Storing the study's linkage key in a password-protected and VCU-approved storage location (see <https://dms.vcu.edu>)
- When analyzing particularly sensitive information, using computers that are unconnected from the internet.
- Proper destruction of electronic records (and obtaining prior permission when required) in accordance with VCU Records Management policies
- Other protection not listed in this question – describe below

4. * Protections for computers and research devices/apps provided for participant use by the study:

- Transferring data promptly from the device/app to a VCU storage location
- Setting strong passwords on computers and research devices (when applicable)
- When providing devices or mobile apps to children, informing parents about the settings and how to manage them (if applicable), internet access, and any other installed apps on the device
- Other protection not listed in this question – describe below
- N/A – no computers or devices/apps being provided for participant use

5. * Protections for email/online communications

- Only using VCU/VCU Health email addresses for study-related communications
- Only using VCU/VCU Health-approved methods of teleconferencing or video conferencing (e.g. Zoom) (for studies involving HIPAA, contact VCU or VCU Health Information Security [as appropriate] about HIPAA-compliant systems)
- Other protection not listed in this question – describe below

N/A – no email/online communications

6. * If "other protections" was selected in one or more of the questions above, specify where this study's paper and electronic research data and/or physical specimens will be stored and how they will be secured from improper use and disclosure.

Paper based records will be kept in study three ring binders that are stored in large upright locked cabinets in a locked room and only accessed by authorized study personnel.

All computers and storage devices will be kept in locked cabinets and/or within locked laboratory rooms. Electronic records will be made available only to those personnel in the study through the use of access controls (passwords). Identifiers will be removed from study-related data, and data will be coded with a key stored in a separate, secure location. Electronic data (with study IDs only) is stored in RedCap and/or in Excel spreadsheets that are saved either on hard drives and/or a VCU server. Data from the online registry, as well as the in-person screen and from sessions will be stored in and can only be accessed through the password secured system RedCap. Only approved CBPL/CSTP staff, faculty, and students will have keys and/or electronic access to access this information.

Plasma samples are labeled with participant code numbers and stored in a -80 freezer in a locked laboratory space. The samples are stored separately from identifying information (consent forms).

We are working with HASTech to develop a data security management plan.

7. * If research data that contains any of the 18 HIPAA identifiers will be released to person(s) or group(s) outside of the VCU study team or the PI's department, identify the data recipient(s) along with their VCU department or other institutional or organizational affiliation(s).

Data with identifiers will not be released to any person or group outside of the study team.

8. * Select all identifiers that will be collected as part of this study (including for recruitment, data gathering, data analysis, etc.), even if the data will eventually be anonymized:

- Names**
- Geographic Locators Below State Level**
- Social Security Numbers**
- Dates (year alone is not an identifier)**
- Ages over 89 (age under 89 is not an identifier)
- Phone Numbers**
- Facsimile Numbers
- E-mail Addresses**
- Medical Record Numbers
- Device Identifiers
- Biometric Identifiers
- Web URLs
- IP Addresses
- Account Numbers
- Health Plan Numbers
- Full Face Photos or Comparable Images
- License/Certification Numbers
- Vehicle ID Numbers
- Other Unique Identifier
- No Identifiers
- Employee V#

9. * If the study will code (i.e. de-identify) the research data by replacing subjects' names with assigned subject IDs, explain the following aspects of the coding process:

- **The process for how subject IDs will be generated/assigned (e.g. random, sequential)**
- **Whether there will be a key that links the subject ID with direct identifiers.**

If a key will be created, describe

- **The place where the key will be stored**
- **The role(s) of all individuals who will have access to the key**
- **When the key will be destroyed**

See the help text for guidance.

Data are identified by numeric code only. Participants' names are not directly linked to data. Briefly, a numeric code is assigned to each participant when they provide informed consent, and the numeric part of the code relates to the order in which the individual consented. This participant numeric code appears on all subsequent documents/data forms. A key is maintained in the study binder so the we can demonstrate that a particular data set is associated with a particular consent document. The key and consent documents are stored separately from each other and separately from all data (under double lock or in RedCap). Access to the key and the consent documents is restricted to study investigators, staff, and students: these individuals perform the informed consent and conduct the study with the participants so they already know who the participants are and observe the participants as data are collected. Data keys will be destroyed at the end of the study once the minimum time required for data retention has been met per VCU Data Retention Policy and/or sponsor retention requirements. De-identified data may be stored indefinitely.

Data Retention

1. * Select all of the ways that individually identifiable information obtained during pre-screening and/or screening will be handled for individuals who DO NOT qualify for the study:

- Immediately destroy the information and identifiers (no data collected)
- Immediately destroy the identifiers connected with the data (anonymization)
- Store until the end of study & then destroy
- Use as "screening failure" data by members of the study team
- Provide to others outside of the research team (with the participant's permission)
- Request permission from participant to maintain and use the identifiable information
- Other
- N/A - study does not require screening procedures

2. * Will participants be able to withdraw their data (paper, electronic, or specimens) from the study (e.g. ask that it be destroyed or returned) if they no longer wish to participate? (FDA-regulated studies should select No - see help text)

- Yes
- No

3. If Yes, describe the process (oral, written, email, letter, etc.) that participants should use to request withdrawal of their data/specimens. Identify if there is a timepoint when withdrawal will no longer be an option and/or if the amount of data that can be withdrawn is reduced at different points in the study.

If any participant wants to withdraw his or her data, he can contact the PI, who will work with staff to remove all of the participant's data. Participants will be able to do this at their convenience via phone, email, or in-person.

4. * What will happen to the research materials (e.g. data, specimens, documents, etc.) when the research has been completed?

- Stored indefinitely with identifiers removed
- Stored indefinitely with identifiers attached
- Destroyed at the end of study once the minimum time required for data retention has been met per VCU Data Retention Policy and/or sponsor retention requirements
- Destroyed when notified by sponsor but not less than the minimum time required for data retention per VCU Data Retention Policy
- Other

Sharing Plan

This page addresses times when investigators may be required to share information about participants or may desire to share their research information/specimens with the aim of advancing science. This page creates a plan for when and how information/specimens could be shared.

Try to anticipate all reasonably foreseeable sharing so that the consent document can also reflect that information. However, it is acceptable to amend this page later and explain either how re-consent of previously and currently enrolled participants will occur or why re-consent should not be required.

The IRB reviews this page against the consent document (if one exists) to demonstrate the ethical principle of Respect for Persons by confirming that plans for sharing do not go against what participants would understand about the use of their data/specimens.

The IRB also ensures there are adequate protections for the privacy of participants and the confidentiality of participants' data/specimens when data is shared with others.

1. * Is it likely investigators could discover information about child/elder abuse or neglect that would require mandatory reporting by the investigators or staff?

The Code of Virginia requires that most medical personnel and all employees of institutions of higher education report suspected child/elder abuse or neglect.

- Yes
 No

2. * Will the sponsor or investigator obtain a Certificate of Confidentiality for this study?

Certificates of Confidentiality (CoC) are issued by the National Institutes of Health (NIH), the FDA and CDC to protect identifiable research information from forced disclosure. All human subject research studies regardless of funding can qualify to receive a CoC. A CoC is automatically issued for research that was ongoing on December 13, 2016, or initiated after that date. For more information, see <https://humansubjects.nih.gov/coc/>

- No - Will not obtain CoC for this study
 Yes - CoC has been obtained or issued automatically
 Yes - CoC request is pending
 Yes - Plan to submit request for CoC and will amend study/ICF once status of request is known

3. * Select the way(s) that individual-level information or biospecimens (including DNA) may be used by the VCU PI or VCU study team for other future research projects (i.e. analyses beyond/apart from the aims of this study)?
See help text for definitions.

Will use directly identifiable information or specimens.

- (*'Directly identifiable' means that identifiers like name, medical record number, social security number, etc. are included in/attached to the dataset/specimens. Maintaining identifiable data for future research is treated as a registry by the VCU IRB. The IRB must approve the new research use in an amendment to this study or as part of a new study before the project is initiated. You will be asked more questions about this on a later page*)

Will use de-identified or indirectly identifiable information or specimens.

- (*'De-identified' means that a linkage/key code exists that links identifiers to data/specimens. When the researcher holds both the data and the key, the VCU IRB considers the subjects to be readily identifiable. Maintaining identifiable data for future research uses is treated by the IRB as a registry. The IRB must approve the new research use in an amendment to this study or as part of a new study before the project is initiated. You will be asked more questions about this on a later page*)

Will use anonymized information or specimens.

- (*'Anonymized' means that 1) no linkage/key codes exist that link identifiers to data/specimens; and 2) subjects cannot be readily identified, i.e. no direct or indirect identifiers or identifiable combinations of variables. The VCU IRB considers uses of anonymized data/specimens to not be human subject research.*)

Will use aggregate results (summary-level results), not individual-level information or specimens.

- (*The VCU IRB considers uses of aggregate data to not be human subject research because there are no individual subjects.*)

- Will contribute to an existing registry or repository
(*You will be asked more questions about this on a later page.*)

- Will not use information/specimens for purposes beyond this study.

- Not sure and will submit an amendment when known

- Other use(s) of individual-level information in a way not listed above

4. * Select the way(s) the VCU PI/study team may share individual-level information or biospecimens (including DNA) with other researchers who are not on this study team (i.e. for analyses beyond/apart from the aims of this study).
See help text for definitions.

Will share directly identifiable information or specimens with other researchers.

- (*'Directly identifiable' means that identifiers like name, medical record number, social security number, etc. are included in/attached to the dataset/specimens. Maintaining identifiable data for future research uses is treated by the VCU IRB as a registry. The data recipient's use of identifiable data would require them to obtain IRB review. You will be asked more questions about this on a later page.*)

Will share de-identified or indirectly identifiable information or specimens with other researchers.

- (*'De-identified' means that a linkage/key code exists that links identifiers to data/specimens. The VCU researcher maintains the key but does not share it with any other researchers. The recipient's use of de-identified data/specimens may not be human subject research if there is documentation that the key will never be shared with the recipient, but they should check with their own IRB about review requirements. You will be asked more questions about this on a later page.*)

Will share anonymized information or specimens with other researchers.

- (*'Anonymized' means that 1) no linkage/key codes exist that link identifiers to data/specimens; and 2) subjects cannot be readily identified (i.e. no direct or indirect identifiers or identifiable combinations of variables). The VCU IRB considers uses of anonymized data/specimens by other researchers to not be human subject research, but the recipient should check with their own IRB about review requirements.*)

Will only share aggregate results (summary-level results), not individual-level information or specimens.

- (*The VCU IRB considers uses of aggregate data to not be human subject research because there are no individual subjects. The data recipient should check with their own IRB about review requirements.*)

Will contribute to an existing registry or repository (You will be asked more questions about this on a later page.)

Will submit data to an NIH genomic data repository (You will be asked more questions about this on a later page.)

Will not share information/specimens with other researchers.

Not sure and will submit an amendment when known

Other sharing of individual-level information with other researchers

5. * The Principal Investigator certifies that after the study has been closed with the VCU IRB, the following conditions will be met whenever individual level research information and/or specimens are used or shared:

- The identities of participants who are represented in the dataset/specimens will not be readily ascertainable or otherwise re-identifiable by the recipient;
- If a linkage/code key is created, it will be maintained at VCU and not shared with the recipient under any circumstances;
- The PI will have no knowledge that the remaining information could be used alone or in combination with any other information to identify the individuals represented in the data; and
- The PI agrees to abide by this sharing plan even after the study has been closed with the VCU IRB.

Yes

No

N/A - No sharing will occur

6. If the Certificate of Confidentiality has been obtained by the PI, upload it here:

Pertinent and Incidental Findings

1. * **Is it likely investigators could discover a participant's previously unknown condition (e.g. pregnancy, disease, suicidal thoughts, wrong paternity, genetic results, or other findings that may be of importance to health or well-being) or if a participant is engaging in illegal or reportable activities:**

- Yes
 No

2. * **Describe what possible pertinent or incidental findings stemming from research-only procedures may be discovered.**

During screening, we assess blood pressure. If a participant's blood pressure is high, our study nurse advises the participant to talk to their own doctor and to get treatment.

Participants will have to report marijuana usage as part of the screening process. Although this is an illegal activity, the research staff will not take any actions. If funded, this study will be automatically issued a certificate of confidentiality, which may provide additional protections for participants.

We will ask about respiratory and gastrointestinal symptoms at screening and before each session begins. Answers given at the beginning of each session will be compared to the participants' previous answers, and if any symptoms have increased, Dr. Lipato will be asked to review the symptoms. In some cases, we may contact Dr. Lipato to determine if a session can proceed.

3. * **Explain what actions or procedures research personnel should take to inform the PI of such a discovery :**

Female participants will be tested for pregnancy during the in-person screening visit. If a female participant has a positive pregnancy test, she will be counseled by the study nurse to seek prenatal care.

Regarding respiratory and gastrointestinal symptoms, answers given at the beginning of each session will be compared to the participants' previous answers, and if any symptoms have increased, Dr. Lipato will be asked to review the symptoms. In some cases, we may contact Dr. Lipato to determine if a session can proceed.

4. * **Will findings be disclosed to participants and/or any other person/group outside of the study team?**

- Yes
 No

5. * **Describe a communication plan addressing:**

1. **What criteria will be used to determine which pertinent and/or incidental findings will be communicated, including the following for health related findings:**

- The reliability of the tests/images, such as being done in a CLIA-certified lab,
- Whether the meaning and significance of the findings are known,
- Whether the findings reveal a significant risk of a serious health condition,
- Whether there is an accepted treatment for the health condition revealed by the findings, and
- The risks both of knowing and not knowing the findings, including risks to family members from genetic testing results.

2. **What information will be provided during the consent process about the plans for communicating pertinent and/or incidental findings;**

3. **Whether the participants will be given the option of refusing communication of some or all types of pertinent and/or incidental findings to themselves, their family members, and/or any other individuals or groups; and**

4. **To whom and by whom the findings will be communicated, when, and how.**

Findings for blood pressure and pregnancy will be communicated to participants verbally during the in-person screening visit. These findings will only be communicated to the participant and will be communicated by the study staff conducting the screening. In the event of high blood pressure or a positive pregnancy test, the study nurse will communicate this information and advise the participant to seek treatment.

The reliability of the blood pressure monitor is not known, nor is the reliability of the pregnancy tests we use.

The blood pressure measurement could reveal a significant health risk, depending on how high it is.

There is accepted treatment for high blood pressure.

There are no risks to knowing or now knowing about high blood pressure or pregnancy.

Participants do not have the option of refusing communication about their blood pressure reading or pregnancy test results.

Any adverse events may be reported to the study sponsor at FDA/NIH as needed/per their request. Any information about adverse events reported to individuals outside of the study team will not include participants' names, DOBs, or other identifying information. Currently, the consent form indicates that such data might be shared with the study sponsor:

"Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study:

- The study Sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System
- Officials of the Department of Health and Human Services"