Establishing the Effect of Flavor on the Addictive Potential of Electronic Cigarettes

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HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:
Establishing the effect of flavor on the addictive potential of electronic cigarettes

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1.0 Objectives

1.1 Study Objectives

The current proposal aims to establish proof-of-concept that neural cue-reactivity can serve as an early, objective marker of electronic cigarette (ECIG) addictive potential. Further, this proposal will examine the effect of flavor and nicotine concentration on the addictive potential of ECIGs to aid research informing U.S. Food and Drug Administration (FDA) flavor regulations and smoking cessation.

The specific aims of the study are:
Aim 1: Determine if smokers and e-cigarette users have pre-conditioned neural cue-reactivity to tobacco or fruit-flavored ECIG odors.

Aim 2: Examine the effect of flavor and nicotine on ECIG odor cue-reactivity after conditioning.

Aim 3: Determine if strawberry vanilla flavor results in stronger cue-reactivity than tobacco flavor. Hypothesis: We expect the group assigned to the 18 mg/ml strawberry vanilla flavor to show larger increases in neural cue-reactivity to their assigned odor than the 18 mg/ml tobacco flavor group.

1.2 Primary Study Endpoints

The primary study endpoint is odor cue-reactivity. Functional magnetic resonance imaging (fMRI) will be used to measure neural cue-reactivity to the ECIG odors presented in the study.

1.3 Secondary Study Endpoints

The secondary study endpoints are cigarette dependence, ECIG dependence, ECIG liking and satisfaction, and flavor liking.

2.0 Background

2.1 Scientific Background and Gaps

There is growing evidence that ECIGs can help smokers reduce the number of cigarettes they smoke per day or quit completely.[1-4] Regular ECIG users report that the variety of flavors, like fruit and dessert flavors, help to curb cigarette cravings and maintain abstinence.[5 6] These reports are supported by population data showing that smokers who use flavored ECIGs smoke fewer cigarettes than those who use unflavored or tobacco-flavored ECIGs.[7] Along with the potential for flavors to help smokers switch to ECIGs, appealing flavors have also been identified as a primary contributor to the initiation of ECIG use among youth, which could result in a new generation of nicotine users. The FDA is calling for more information on how flavors affect the addictive potential of ECIGs to determine if flavor is a necessary feature for satisfying adult smokers. However, there remains a critical need for new, innovative methods of measuring the addictive potential of tobacco products that can predict use behaviors.[8]

Compulsive drug-seeking behavior is known to be driven by neuroadaptations in the brain that can serve as early markers of addiction development.[9] A neurobehavioral process that occurs across substances of abuse is the development of conditioned reactivity to drug cues.[10] Drug cues alone can elicit craving, drug-seeking behavior, and relapse.[10 11] Cue-reactivity is mediated by neuroadaptations in mesocorticolimbic circuitry that occur when environmental and sensory stimuli become associated with the dopaminergic effects of the drug.[12-14] Physiological cue-reactivity has been found to develop after only 11 pairings between environmental cues and smoking.[15] Using functional magnetic resonance imaging (fMRI), our group was the first to show evidence of neural reactivity to visual ECIG images among regular ECIG users.6 Given that food-related flavors independently elicit reactivity throughout reward and learning brain circuitry that drives conditioning, fruit and dessert ECIG flavors have the potential to significantly enhance ECIG cue conditioning.[16 17]

2.2 Previous Data

Dr. Foulds and The Penn State Tobacco Center of Regulatory Science (TCORS) team conducted a survey of over 6,000 ECIG users and found that nicotine and flavor play primary roles for former smokers who quit using e- cigs.[5] Most participants used e-liquids with nicotine concentrations between 13 and 18 mg/ml and dependence increased with the level of nicotine concentration.[18] Many participants reported that they switched from cig-a-like devices to advanced devices that deliver more nicotine and offer a variety of flavor options.[19] ECIG users' top-rated flavors fell into 3 categories; tobacco, dessert/sweets, and fruit.[5]

In preliminary fMRI research on the neural effects of ECIG use, we found that ECIG images elicited stronger neural activation throughout the cingulate, temporal, and occipital cortices than the control images of electric toothbrushes and cortical activation to ECIG cues increased after ECIG use.[20 21] Reductions in withdrawal symptoms after ECIG use were associated with changes in resting state functional connectivity in brain networks involved in emotion, cognitive control, visuospatial awareness, and salience, and between reward and executive control networks.[20] Surprisingly, neural connectivity changes were not influenced by the amount of nicotine delivered during ECIG use, which varied widely with participants' personal devices.[20 21] This finding supports our hypothesis that other conditioned features of ECIG use influence neuroadaptations.

The Penn State Center for Nuclear Magnetic Resonance Research (CNMRR) has pioneered the study of human olfaction. Dr. Karunanayaka and his colleagues have shown that the neural olfaction sensory system overlaps with limbic and prefrontal regions involved in associative learning, including the hippocampus, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC).[22 23] They have linked odor to multisensory associative learning that occurs within the olfactory cortex.[17] They were the first to apply their work in olfaction to smoking and found that the smell of fresh tobacco enhances smoking cue reactivity and the perceived enjoyment and reward of smoking.[24 25] Using fMRI, they found that neural cue-reactivity to smoking odors is associated with self-reported control over craving, supporting the role of odor in smoking behavior.[25] This project proposes to use the olfactometer (Emerging Tech Trans inc), a commercially available MRI device developed by researchers at the CNMRR.

2.3 Study Rationale

The proposed study will establish proof-of-concept for using innovative olfaction fMRI cue-reactivity to measure how product characteristics, such as flavor and nicotine, affect the addictive potential of ECIGs. This method can inform FDA regulations on the abuse liability of new flavored tobacco products and provide an early neuromarker of success for smokers attempting to switch from cigarettes to ECIGs.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Aged 21-60
2. Smoke filtered cigarettes/machine-rolled cigarettes (≥5 cigarettes per day) or daily e-cigarette use for past year
3. No serious quit attempt in prior month. This includes use of any FDA approved smoking cessation medication (varenicline, bupropion [used specifically as a quitting aid], patch, gum, lozenge, inhaler, and nasal spray) in the past 1 month as an indication of treatment seeking.
4. Willing to supplement cigarette smoking with ECIG use for 4 weeks or replace e-cigarette with study product for 4 weeks
5. Willing to attend regular visits over a 4-week period (not planning to move, not planning extended vacation, no planned surgeries)

6. Willing to undergo two fMRI scans
7. Able to read and write in English
8. Able to understand and consent to study procedures
9. Access to computer with internet service that allows for use of Zoom

3.2 Exclusion Criteria

1. Impaired smell function as measured via standardized screening assessment
2. Unstable or significant medical condition in the past 12 months (recent heart attack or some other heart conditions, stroke, severe angina including high blood pressure)
3. Severe immune system disorders (uncontrolled Human Immunodeficiency virus infection; unstable multiple sclerosis symptoms), respiratory diseases (exacerbations of asthma or chronic obstructive pulmonary disorder, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis), or any medical disorder/medication that may affect participant safety or biomarker data
4. Women who are pregnant (verified by urine pregnancy test at any visit), trying to become pregnant, or nursing
5. Medical conditions associated with cognitive impairment or neurological dysfunction
6. Severe claustrophobia
7. Current depressive or anxiety disorder
8. Uncontrolled mental illness or substance abuse or inpatient treatment for these conditions in the past 6 months
9. Use of illicit drugs or prescription drugs for non-medical use daily/almost daily or weekly in the past 3 months per National Institute on Drug Abuse (NIDA) Quick Screen, not including use of marijuana
10. Any known risk from exposure to high-field strength magnetic fields (e.g., cardiac pacemakers), any irremovable metallic foreign objects in their body (e.g., braces), or a questionable history of metallic fragments which are likely to create artifact on the MRI scans
11. Known allergy to propylene glycol or vegetable glycerin
12. Other member of household currently participating in the study
13. History of a seizure disorder or had a seizure in the past 12 months
14. Currently taking or who have taken medications prescribed to prevent seizures (such as Carbamazepine or Phenobarbital). Using seizure medications for off-label use (indications other than treatment for seizures) will not be included as an exclusion, these will be assessed on a case-by-case basis

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

The Principal Investigator reserves the right to remove a participant from the study for any reason, based on their discretion.

Early Withdrawal Criteria Prior to Randomization: Participants who met any criteria below at Visit 2 will be considered for withdrawal prior to randomization:

1. Starting nicotine replacement therapy (e.g., patch, gum, lozenge, inhaler, nasal spray, Zyban, Chantix)
2. Use of other non-cigarette tobacco products in the past 7 days
3. Reporting a quit attempt in the past 7 days
4. Participant is not able to attend their Visit 2 Randomization visit within the study window.

General Withdrawal Criteria

1. Missing their study visit window: If a participant misses their study visit window, the participant will be considered for withdrawal from the study.
2. Not maintaining ECIG and cigarette use diary
3. New pregnancy: Participants who report a new pregnancy at any point during the study will be withdrawn.
4. Suicide attempt: If at any time during the study it is discovered that a participant has made a suicide attempt, they will be withdrawn from the study.
5. Cardiovascular disease (CVD) event requiring inpatient hospitalization: CVD typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
6. DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system) requiring inpatient hospitalization.
7. Psychiatric Inpatient Hospitalization: A participant will be withdrawn if he/she reports an inpatient hospitalization for psychiatric reasons at any time during participation in the study.
8. Participant choice: Participants may choose to remove themselves from the study by informing the research team in writing, by phone call or in person at any point during the study. If they choose to remove themselves from the study, they will not receive any further contact from the study center.
9. Adverse events related to ECIG use: Adverse events will be monitored at every study visit.
10. Worsening substance abuse in which the participant is behaving inappropriately at visits or demonstrates an inability to continue with the study.
11. Any inpatient hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical professional to determine whether continued participation in the study is appropriate (this could include recovery from a major surgery, worsening of psychiatric symptoms, etc).
12. Any situation where participant is not able to use their ECIG for a period of more than 2 weeks (e.g. incarceration or other similar situation) unless they report not using the ECIG by choice.
13. Participant behavior: If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, appears/admits to giving away/selling study products, consistently loses study products etc., then the PI can withdraw him/her from the study at the PI's discretion.

3.3.2 Follow-up for withdrawn subjects

If participants are withdrawn from the study for any of the reasons noted above prior to randomization, they will be replaced until a total of 56 participants have been randomized to the study. Reasons for withdraw will be ascertained from subjects who withdraw from the study. In addition, among all participants who choose to withdraw, we will attempt to confirm their withdrawal and reason for withdrawal in writing (via mail or email).

4.0 Recruitment Methods

4.1 Identification of subjects

All recruitment for this study will be routed through IRB STUDY00002213 which will also serve as the initial recruitment point of contact.

4.2 Recruitment process

4.2.1 How potential subjects will be recruited.

Interested volunteers calling the study center number will first complete the eligibility script and questions for IRB STUDY00002213 (screener 1). If a participant's responses match this study's specified inclusion criteria they will be forwarded to research staff for further phone screening (phone screener 2). Subjects that were unable to be reach by phone will have an email sent to them asking them to contact us via email or phone. A draft of the email will be uploaded to CATS.

Recruitment materials are included in IRB STUDY00002213.

4.2.2 Where potential subjects will be recruited.

Refer to IRB STUDY00002213 Call Routing Screener.

4.2.3 When potential subjects will be recruited.

Starting 2019 and running till 2024.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB.

[*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

Verbal informed consent will be collected over the phone prior to screener 2. Potential eligible participants will be invited to take part in a remote visit where additional eligibility screening will occur. Written informed consent will be obtained before in-person randomization/MRI visits will begin.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☒ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** ***[Complete Section 5.5]***

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Screening portion: Subjects will have the screening portion of the study explained to them in detail over a phone call. They will have the opportunity to ask any questions and then will be asked to give their verbal consent to take part in the screening portion.

Randomization/MRI portion: When participants attend their remote screening visit, they will have the study explained to them in detail, and be given a long form consent form to look over before their in-person MRI visit. They will have the opportunity to ask questions at both visits and then will be asked to sign their consent form at the in-person visit. .

5.2.2 Coercion or Undue Influence during Consent

Once potential study volunteers are identified, they will be given information about the study and offered the opportunity to participate. The researchers obtaining consent will be instructed to clearly indicate that the participant's enrolling in the trial is purely voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not. Given the number of contacts and visits involved in the study protocol, the compensation provided to the participant is modest.

5.3 Waiver of Written Documentation of Consent

5.3.1 Indicate which of the following conditions applies to this research:

☒ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Participants who are interested in the study will be asked to consent to allow the researcher to pre-screen them for the study over the phone and/or Zoom by asking all screening questions of all participants (eligible or ineligible). Participants will be asked if this information can be retained so that the study team will know reasons that participants are not eligible for the study.

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

Verbal script will be used as found "Phone Screener," which is found in the supporting documents.

The written consent process will be documented in writing as follows::

- The current IRB approved long form written consent form will be used.
- The subject will sign the consent form during their in-person visit after all of the screening has taken place.
    - A copy of the consent form will be provided to the subject/representative. Whenever possible the consent form will be provided to the subject in advance of the consent discussion.

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

5.4.1 Indicate the elements of informed consent to be omitted or altered

N/A

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

N/A

5.4.3 Describe why the research involves no more than minimal risk to subjects.

N/A

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.4.6 Debriefing

N/A

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

N/A

5.5.2 Describe why the research involves no more than minimal risk to subjects.

N/A

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

N/A

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

N/A

5.5.5 Additional pertinent information after participation

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

N/A

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

N/A

5.6.2.2 Adults Unable to Consent

N/A

5.6.2.3 Assent of Adults Unable to Consent

N/A

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

N/A

5.6.3.2 Assent of subjects who are not yet adults

N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☒ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

All study data will be retained indefinitely.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

The study phone screener (phone screener 2) will be used to check eligibility criteria (date of birth), and when participants are screened, their contact information will be used to follow-up about scheduling and for appointment reminders. This requires that we have complete contact (name, phone number) information.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

In order to screen the participants prior to inviting them into the study center, the investigators are conducting a phone screening to determine if the participants are likely to be eligible for the study.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

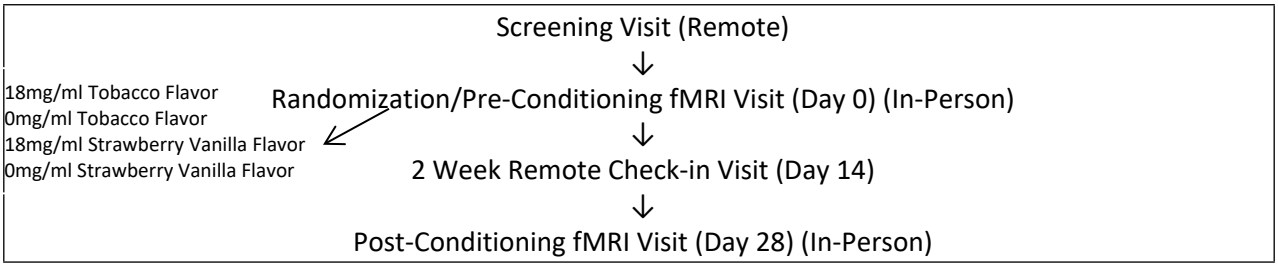
The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This study is a one-site, four-arm, parallel group randomized controlled trial (RCT).



7.2 Study Procedures

7.2.1 Phone Pre-Screening

Before scheduling remote screening visit, all participants will complete initial screening questionnaires. First, participants will be directed to complete a short survey (online or over the phone) to determine eligibility for the study as part of the call routing screen protocol #2213 (Screener 1). If their information indicates potential eligibility, they will be contacted to complete Phone Screener 2 (a longer and more in-depth screening for the specific study) which is completed over the phone. Once the participant is determined eligible from Screener 2, remote screening visit will be scheduled where participants will complete the Visit Screener to determine final eligibility.

7.2.2 Final Screening Visit - Remote Visit

A Penn State Health Zoom meeting link will be emailed to participant for the previously scheduled time along with a PDF copy of the long form written consent.

Participants who meet preliminary eligibility criteria on the phone screen (Screener 2) will complete more in-depth screening measures on their smoking, substance use, medical, and psychiatric history via interview and computerized questionnaires via Zoom. Additionally, a CCQ (Clinical COPD Questionnaire, 10 items) will be administered to allow the pulmonologist on the study team to review changes in health status to lung function, degree of dyspnoea and (change in) functional capacity. This will be administered at all study visits. Participants will then complete the B-SIT test At the conclusion of the visit, eligible participants will be instructed to abstain from using any tobacco products for 14 hours prior to the next visit. Participants will also be instructed to eat before their next visit. Cigarettes per day will be recorded on a daily log and participants will receive a daily REDCap survey link via text message using the Twilio service to enter their use information daily. Participants will be instructed on how to complete the survey. Participants who are unable or unwilling to receive study text messages will track their cigarette use on the paper log only and report their use the researchers at each contact. All participants will be given a manual on how to use the study provided e-cigarette to review before being given the study device at their next visit.

7.2.3 Randomization/Pre-Conditioning fMRI Visit (Day 0) – In Person/Remote

Participants will sign their long form written consent at this visit prior to any further study procedures.

Exhaled breath CO (eCO) will be measured at the start of the visit. A urine sample will also be collected and tested for cotinine using the NICCheck cotinine test and pregnancy if participants are of child bearing potential. Eligible participants will then be randomized to one of the four conditions and asked to complete the baseline assessments. This includes the standardized smell test (B-Sit), adverse events assessment and computerized questionnaires of cigarette use, cigarette dependence, liking, and withdrawal as indicated in Table 1. Some of the measures can be done remotely via Zoom, others will need to be completed in person. The remote assessments will be conducted via a Zoom session within 3 days following the scheduled in-Person MRI. The remote visit will only occur after written consent has been obtained. This is being done to limit the amount of face-to-face time during study visits.

Then, participants will complete the fMRI odor cue-reactivity task in the MRI scanner lasting approximately 45 minutes. During the scan, participants will be administered four flavors in separate 4 minutes blocks for eight runs. The flavors will be delivered to the participant's nostrils via tubing from the olfactometer machine. The release of the flavors will be timed with participants' natural rate of respiration and randomized across blocks. At the end of this visit participants will be given the ECIG device and 4-week supply of their randomly assigned flavor cartridges (approximately 2 cartridges/day) and instructed on how to use the device. Participants will be instructed to take at least 50 puffs per day from the ECIG device to replace conventional cigarette smoking. The participant will be instructed to bring back all used and unused cartomizers to the study center. ECIG puffs per day and cigarettes per day will be recorded on a daily log. Participants will receive a daily REDCap survey link via text message using the Twilio service. Participants will be instructed on how to complete the survey and will be provided with a paper log to tally their cigarette use throughout the day. Participants who are unable or unwilling to receive study text messages will track their cigarette use on the paper log only.

7.2.4 Conditioning Phase Check-in Visit (Day 14 ± 7 days) - Remote

Participants will take part in a remote visit via Zoom to report their ECIG use and cigarettes per day (CPD) (collected in the daily logs. Participants will complete the measures outlined in Table 1. Participants will complete an adverse events assessment and discuss challenges to using their e- cig daily and study staff will assist in problem solving barriers to compliance. At the end of the visit participants will be instructed to remain abstinent from all tobacco products including their ECIG for 14 hours prior to the next study visit and to eat before their next study visit.

7.2.5 Post-Conditioning fMRI Visit (Day 28 ± 7 days) – In Person/Remote

Participants will attend a final visit to complete biomeasures, computerized surveys, the adverse events assessment, and the same fMRI tasks as the baseline MRI visit as indicated in Table 1. Some of the measures can be done remotely via Zoom, others will need to be completed in person. The remote assessments will be conducted via a Zoom session ± 3 days of the scheduled in-Person MRI. This is being done to limit the amount of face-to-face time during study visits. eCO will be measured and urine will be collected for cotinine and pregnancy tests. At the end of the visit, participants will be debriefed and counseled on smoking cessation. All participants will be given a copy of the Surgeon General's booklet 'How Tobacco Smoke Causes Disease' **(SEE ATTACHMENT: Surgeon General's Booklet).**

Table 1: Measures Table (Black X – In Person; Green X – Remote)

	Final Screening	Randomization/ Pre-Conditioning fMRI	Check-In	Post-Randomization fMRI
Visit	**1**	**2**	**3**	**4**
Day	**-7**	**0**	**14**	**28**
QUESTIONNAIRES				
Visit Screener	X			
Tobacco Use History	X			
Name Registry	X			
MRI Safety Form	X	X		X
Demographics	X			
Medical History	X			
Concomitant Medications	X	X	X	X
Adverse Event Assessment		X	X	X
Cigarette Details	X			
CCQ (Clinical COPD Questionnaire)	X	X	X	x
Alcohol Audit-C	X			
NIDA Quick Screen	X			
Environmental Smoke Questionnaire	X			
MINI Psychiatric Interview	X			
Daily Smoking and ECIG Use Logs	X (cigarette only)	X	X	X
Cigarette Dependence (Fagerstrom and Penn State Cigarette Dependence Index)		X	X	X
Minnesota Withdrawal Scale		X	X	X
Craving		X	X	X
Cigarette liking scale		X	X	X
ECIG Use History	X	X	X	X
ECIG evaluation scale			X	X
ECIG Side Effects			X	X
ECIG dependence			X	X
ECIG Perceived Health Risk			X	X
ECIP Patterns of Use			X	X
Perceived Benefits and Harms of Using ECIG		X		X
PROCEDURES				
B-SIT Smell Test		X		
fMRI Cue-Reactivity Task in Scanner		X		X
BIOMEASURES				
Pregnancy Test		X		X
Exhaled CO		X		X
Urine Sample Collection		X		X
NICCHECK Rapid Cotinine Test		X		X

7.2.6 Adverse Event Reporting

Adverse events (AE) will be monitored at every study visit after Visit 1. This will be done by asking participants if they have experienced any new or worsening symptoms. If the participant indicates a new or worsening symptom, an adverse event form will be completed. This form will document the date of AE report, the start and end date of the symptom, a description of the AE, the outcome, the severity, and the action taken to resolve the symptom. Finally, it will be determined by the medical monitor if the symptom is related to the study.

7.2.7 Appointment Reminders

Phone call reminders will be used throughout the study to remind participants of their visit (approximately two days prior). Also, screening visit confirmation and directions will be

emailed/mailed to the participant prior to Visit 1. **(SEE ATTACHMENT: First Appointment Reminder and Appointment Phone Call Text).**

7.2.8 Daily Dairies for ECIG and Cigarette Use

Prior to randomization, participants will be asked to track the number of cigarettes smoked per day using a paper daily diary. They will also receive a daily REDCap survey link via text message (through Twilio) to enter their cigarette usage. During the 4-week ECIG conditioning period, participants will be required to record their ECIG use (in puffs per day) and the number of cigarettes smoked. A paper-based daily diary designed for data collection of each product type will be used. Participants will also continue reporting their use via REDCap survey links each evening. Research assistants will review the data entered by participants via the REDCap survey links at each visit. If participants did not complete the survey online, the researcher will ask the participant at each visit their ECIG and cigarette use. The diary will be used as a memory aid for the participant. (**SEE ATTACHMENT: Cigarette Pack Daily Dairy and E-cigarette and Cig Daily Diary**)

7.2.9 MRI Scan Details

The 45-minute MRI scan will begin with a 10-minute T1-weighted high resolution anatomical scan and a 5-minute resting state scan, followed by the odor cue-reactivity functional task. Scans will be conducted on a Siemens 3T Prisma-Fit scanner (Siemens Healthineers, Erlangen, Germany) equipped with a 64-Channel head coil. Functional images will be collected through T2*-weighted interleaved ascending multiband EPI acquisition in 2.85 x 2.85 x 4mm resolution and slice thickness (TR=600ms, TE=30 ms) with a field of view of 230mm, 80x80 matrix size, and 50° flip angle.

7.2.10 Flavor-Cue Reactivity Details

The olfactometer (ETT, inc: http://www.emergingtechtrans.com) will be used to deliver the e-liquid odors to the nose during a respiration-triggered event-related fMRI cue-reactivity task. The tobacco and strawberry vanilla e-liquid flavors, as well as two common control scents, Lavender and PEA (phenyl ethyl alcohol; that smells like rose), will be delivered in randomized order during 4-minute blocks over 8 runs. The flavors will be delivered for 4 seconds every 20-30 seconds depending on respiration rate. At the end of the task, participants will be delivered each odor again and asked to rate how much they like the flavor using a fiber-optic button box.

The lavender odor is an experimental control condition that encourages participants to maintain attention and task engagement during the MRI scan. It provides us with a quality control manipulation, whereby if we suspect from poor data quality that a participant was not paying attention in the scanner, we can confirm this if they were also not responding to the lavender scent as instructed.

7.3 Duration of Participation

All participants will be in the study for a period of at least 5 weeks but no more than 8 weeks and will attend 2 in-person clinic visits at the study center. The randomization/pre-conditioning visit (Visit 2), remote check in (Visit 3) and post-conditioning visit (Visit 4), will happen within a 4 week period.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

The ECIG used will be the EGO ECIG. Previous work has shown that the EGO ECIG was capable of delivering nicotine to its users.[26] This ECIG is made up of 2 parts, a battery and a cartomizer. The cartomizer contains the heating element and the liquid. The liquid used in the cartomizer will contain either 0 mg/ml or 18 mg/ml of nicotine and be either tobacco or strawberry vanilla

flavor. The nicotine concentration in the liquid and the flavor will be determined by random assignment. The cartomizers will be filled with liquid by the researchers and will be used once by the participant and returned to researchers.

7.4.2 Treatment Regimen

Participants will be randomized to one of four conditions:

- Tobacco flavor ECIG (18 mg/ml nicotine concentration)
- Tobacco flavor ECIG (0mg/ml nicotine concentration)
- Strawberry Vanilla flavor ECIG (18 mg/ml nicotine concentration)
- Strawberry Vanilla flavor ECIG (0mg/ml nicotine concentration)

Participants will be instructed to use their ECIG for at least 50 puffs per day to replace conventional cigarette use.

7.4.3 Method for Assigning Subject to Treatment Groups

Blocked randomization stratified across gender and matched for age will be accomplished with a 1:1:1:1 ratio of condition assignments with a goal of 56 randomized over a 7 month recruitment period. The randomization list will be stored in a password protected document that will only be accessed by unblinded study personnel.

7.4.4 Subject Compliance Monitoring

The importance of honest reporting will be stressed to participants. Compliance to the instructions for ECIG use will be determined by the daily diary procedure and the amount of product used. Unused products will be collected, weighed, and recorded. We emphasize that compliance issues should be minimal given the fact that participants remain in the study while continuing to use conventional tobacco cigarettes.

7.4.5 Blinding of the Test Article

The study ECIGs will be received by unblinded study staff. Unblinded staff will appropriately package the cartomizers and ECIG parts into packs/kits for the participants. The kits will be assigned numbers and the participants will be randomly assigned the kit number at the randomization visit (Visit 2). The blinded research assistant will not be involved in the packing and labelling of the kits. The blinded research assistant will be told what participant is assigned to which kit, which will maintain the blind.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The ECIG will be purchased online in its standard packaging and shipped to Penn State. Empty cartomizers also will be purchased online. The ECIG liquid will be purchased from reputable online ECIG liquid vendors.

7.4.6.2 Storage

All study products (ECIG batteries, cartomizers, liquid) and components will be stored in a locked closet away from light, heat, and moisture.

7.4.6.3 Preparation and Dispensing

The unblinded study staff will be responsible for filling the cartomizers with the appropriate nicotine concentration (0mg/ml or 18 mg/ml) and flavor (tobacco or strawberry vanilla)in a biological safety cabinet. Filled cartomizers will be stored in bottles/bags with child-proof caps. Once filled, unblinded staff will then put cartomizer-containing bottle into ECIG kits

labelled with unique identifiers in order to track bottles and maintain blinding. Unblinded staff will appropriately package kits for the participants. At the randomization visit (Visit 2), participants will be randomly assigned a Randomization ID that matches a kit number. The blinded research assistants will not be involved in the packing and labelling of the kits. The blinded research assistant will be told what participant is assigned to which Randomization ID, which will maintain the blind.

7.4.6.4 Return or Destruction of the Test Article

Participants will be permitted to keep their ECIG device at the end of the study. Participants will be required to return all used and unused cartomizers to the research assistant at each clinic visit using provided containers/bags. Participants will not keep unused cartomizers at the end of the study. If a participant is withdrawn for medical reasons (CVD event), they will be asked to return their device/cartomizers via a pre-paid envelope to the study center.

7.4.6.5 Prior and Concomitant Therapy

Concomitant medications will be collected regularly throughout the trial to serve as covariates during analysis and to monitor participant health conditions. Medications related to certain medical conditions that are exclusions to the study, such as COPD and current heart conditions, will serve to alert the study staff of the presence of these conditions during screening.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Up to 75 subjects may be enrolled in this study in order to have 56 randomized subjects. We will continue to consent participants to the study until we reach 56 randomized subjects.

8.2 Sample size determination

For the proposed between-subject analyses, we will be looking for trends in the hypothesized direction, not statistical significance with traditional parametric statistics. With an estimated medium effect size, we will have approximately 50% power to find a liberal between-subject effect ($p<.10$) for the proposed t-test between the flavor groups on baseline cue-reactivity, 60% power to detect changes in cue-reactivity between the nicotine content and flavor groups, and 90% power to detect within-subject changes in cue-reactivity at $p<.05$. Groups will be stratified by gender to estimate gender effects for future research.

8.3 Statistical methods

Images collected during the fMRI odor cue reactivity task will be preprocessed using a standard Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) software pipeline. Blood oxygen level dependent (BOLD) activation during the tobacco, strawberry vanilla, and rose flavors will be modeled using a double-gamma hemodynamic response function, contrasted to one another, and merged across the two runs for each participant. To create images that capture changes from baseline to post-conditioning, a difference z- statistic image will be calculated by subtracting the baseline image from the post-conditioning image. The lavender odor is an experimental control condition that encourages participants to maintain attention and task engagement during the MRI scan. It is not part of the endpoints of the study.

Aim 1: Determine if smokers and ECIG users have pre-conditioned neural cue-reactivity to tobacco or strawberry-vanilla ECIG odors. One- sample t-test will be conducted on the contrast of tobacco > strawberry vanilla, tobacco > rose, strawberry vanilla > rose to identify anatomical brain regions where tobacco elicits greater neural activation over strawberry vanilla and rose odors and strawberry vanilla elicits greater activation over rose odors. We expect tobacco odor to elicit greater activation in the ventral striatum, amygdala, anterior insula, and OFC than the strawberry vanilla and rose for combustible cigarette smokers and tobacco-flavored e-cigarette users. We expect strawberry-vanilla odor to elicit greater activation in ventral striatum, amygdala, anterior insula, and OFC than tobacco and rose for fruit-flavored e-cigarette users.

Aim 2: Examine the effect of flavor and nicotine on ECIG odor cue-reactivity after conditioning. Two-sample t-test will be conducted in FSL for the strawberry vanilla>rose and tobacco>rose odor difference score z- statistic images comparing the 18 mg to 0mg nicotine content ECIG groups. A paired two-sample t-test will be conducted to compare the tobacco>rose and strawberry vanilla>rose odor difference score z-statistic image separately for each 18 mg/ml ECIG flavor group. These t-tests will identify anatomical regions with significant effects of nicotine level and assigned vs. unassigned flavor over time. We expect that BOLD activity in regions implicated in smoking cue-reactivity will increase more over the conditioning phase for the 18 mg nicotine group compared to the 0mg nicotine group and for odors from the assigned vs. unassigned flavor.

Aim 3: Determine if strawberry vanilla results in stronger cue-reactivity than tobacco flavor. A two-sample t-test will be conducted for the assigned flavor (strawberry vanilla or tobacco) > control rose difference score z- statistic images comparing the flavor groups. These t-tests will identify anatomical regions with significant flavor group (tobacco vs. strawberry vanilla) by time (baseline to post-randomization) interaction effects on each odor image. For this analysis, only the 18 mg/ml nicotine content flavor groups will be included.

Exploratory Behavioral Aim: Determine if changes in flavor cue-reactivity are associated with changes in ECIG satisfaction, liking, craving, and dependence. One-sample t-tests will assess for anatomical regions where BOLD changes in odor cue-reactivity are correlated with changes in behavioral measures of e- cig satisfaction, craving, and dependence collected at the 2-week check-in and post-randomization visit, and changes in ECIG liking collected at the baseline and post-randomization visits.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

The study coordinator and the PI will be responsible for the daily oversight of subject safety. Medical history will be reviewed by the study staff, and based on eligibility criteria, any questionable medical histories will be brought to the attention of the medical monitor for final inclusion determination prior to randomization. In a similar manner, contraindications for the treatment products and vital signs will be checked by study staff at each in person visit. The medical monitor will be available via phone for any consultations as necessary.

Participants will be under medical supervision while in the study (i.e., by the medical monitor) and seen on an ongoing basis by our research staff who will document adverse events. The medical monitor will assess all adverse events and will be available for consultation over the phone for urgent matters. Otherwise, the PIs and/or the medical monitor will meet weekly with the study staff to review patient's progress and their experiences with the study products, including any adverse events.

9.2 Data that are reviewed

Data that will be reviewed include:

- Accrual and retention
- Medical history and concomitant medications
- Adverse events and serious adverse events
- Protocol deviations/violations

9.3 Method of collection of safety information

All data, including safety data, will be coded directly into REDCap electronic forms during study visits. Participant adverse events and serious adverse events will be assessed at each in-person study visit and each phone call visit but can be reported at any time during the study.

9.4 Frequency of data collection

Safety data, including adverse events and serious adverse events will be collected at each study contact.

9.5 Individuals reviewing the data

The study coordinator and the PI will be responsible for the daily oversight of subject safety. The PI and/or the medical monitor will meet weekly with the study staff to review participants' progress and their experiences with the study products, including any adverse events. For more urgent and/or serious adverse events, the medical monitor will be available for consultation by phone. The medical monitor will then make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study. Study pulmonologist will review and provide expertise related to CCQ data and all pulmonary AEs.

9.6 Frequency of review of cumulative data

All of the data from the study (including adverse events) will be reviewed by the leadership group, including the PI and the medical monitor, on a regular basis to review patients' progress and their experiences in the study.

9.7 Statistical tests

Statistical methods will be used to analyze the safety data to determine whether harms are occurring. Paired sample t-test (or nonparametric Wilcoxon Rank-Sum test) will be used to examine the changes in the outcome measures (CPD, CO, subjective measures) from the baseline.

9.8 Suspension of research

Due to the low risk of the intervention, it is unlikely that there will be a need to suspend the research. However, should the medical monitor identify any issues after reviewing the data, they can develop stopping rules for the trial, and the recommendations will be followed.

10.0 Risks

10.1 ECIG use:

- There may be some unknown risks related to the use of ECIGs though these risks are not considered to be greater than risks associated with conventional cigarette use.
- The most common side effects associated with using an ECIG are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, sore throat, mouth ulcers, dizziness, headache, and nausea.
- There are reports that some people who use e-cigarettes have experienced seizures, with most involving youth or young adult users. Participants with a history of seizures or take medications to prevent seizures will be excluded from the study.
- There have been some reports of serious lung illnesses among those who used e-cigarettes, and even some cases of death as a result (not all causes of death have been identified). The investigations being conducted by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have found that the majority of people experiencing these

illnesses were using e-cigarette products that contained tetrahydrocannabinol (THC) and/or products that were bought off the street or from other illicit channels and so it is important that participants avoid such products. The e-cigarette products used in this study do not contain THC and were bought from manufacturers where quality testing and control is performed. Nonetheless, participants will be advised to call their doctor immediately if they experience cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, or fever after using their e-cigarette. Participants will be told to only use the e-cigarette and liquid pods (cartridges) given to them by the researchers and to not tamper with their e-cigarette or use other liquids with the e-cigarette device.

- If stored improperly (in pocket or where the ECIG device can turn on accidently), overheating of the device may occur, which presents a minor burn risk.
- Electronic cigarette liquid contains vegetable glycerin, propylene glycol and flavorings. Participants with known allergies to these substances will be excluded in the study. The most common reported allergic reaction to these substances is contact dermatitis.

10.2 Nicotine addiction: Participants may be given a study product that contains nicotine, which is an addictive substance. The amount of nicotine they receive from this product depends on what product they are given and how they use it.

10.3 Nicotine withdrawal symptoms: Smoking fewer conventional cigarettes may result in nicotine withdrawal symptoms (e.g. irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, difficulty concentrating). These symptoms will be monitored bi-weekly.

10.4 New development of pregnant or want to become pregnant: Nicotine, either from cigarettes or from the study product (ECIG), is known to be harmful to the developing human fetus. If you are pregnant or become pregnant, cigarettes and the study product (ECIG) may cause problems to your unborn baby. Women who are pregnant or are nursing a child may not participate in this research study. Females capable of becoming pregnant will be administered a pregnancy test prior to beginning the research. Participants must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation. The investigator will discuss appropriate precautions with participants.

10.5 MRI (Magnetic resonance imaging) Risks: MRI does not involve radiation and there are no known long-term risks of MRI. Participants will be assessed for MRI safety at the screening visit and again at the scan visit before entering the scanner. We will be assessing for potential MRI hazards like metal fragments in the body or metal implanted devices that could shift during scanning. Participants will be instructed to remove all metal from their body and clothing before entering the scanning room. The major discomforts of fMRI scanning include lying still in a supine position for a sustained period of time and hearing loud tapping sound during image acquisition. Participants may be uncomfortable inside the MRI scanner, especially if they do not like to be in closed spaces ("claustrophobia"). In between scanning sequences, participants will be able to talk with the MRI staff through a speaker system. At any time, the participant can choose to stop the scan by squeezing a "panic" button.

10.6 Loss of confidentiality: There is a risk of loss of confidentiality if information is obtained by someone other than the investigators. Precautions will be taken to prevent this including direct coding of data in REDCap.

10.7 Randomization in clinical trials: Participants will be assigned to a research intervention by chance. The research intervention they receive may prove to have more side effects than the other research intervention(s).

10.8 **Incidental Finding:** None of the tests carried out in this study are intended to provide diagnoses for clinical purposes, but participants will be alerted to findings that should be discussed with a healthcare provider (such as high blood pressure or MRI findings). The MRI scans done during this study are NOT designed to detect or evaluate any medical condition. They are intended solely for research purposes. The investigators for this project are not trained to perform medical diagnosis,

and the scans to be performed in the study are not optimized to find abnormalities. On occasion, a member of the research team may notice a finding on a scan that seems abnormal. When a finding is noticed, one of the investigators may consult a physician specialist, such as a radiologist or neurologist, as to whether the finding merits further investigation. If the specialist recommends further follow-up, the investigator or another member of the research team will contact the participant within 48 hours (via a phone call) of the recommendation and suggest that the participant contact his or her private medical provider for follow-up. To facilitate follow-up care, the participant will be given a copy of the images via a letter if the subject would like one. Being told about a finding may cause the participant anxiety as well as suggest the need for additional tests and financial costs. Medical insurance may be affected whether or not the finding is ultimately proved to be of clinical significance. Costs for clinical follow-up will not be covered in the cost of research. Participants will be told that their decision as to whether to proceed with further examination or treatment is their own.

10.9 Questionnaires: It is possible that some of the questions in the questionnaires may make participants uncomfortable. They will be instructed that they are free to skip any questions that make them uncomfortable.

11 Potential Benefits to Subjects and Others

11.5 Potential Benefits to Subjects

There may be a direct benefit to participants in terms of decreased use of conventional cigarettes that are known to be more harmful than ECIGs.

11.6 Potential Benefits to Others

The potential benefit to others is that this research can provide the scientific information needed to regulate tobacco products.

12 Sharing Results with Subjects

This study is not designed to diagnose any disease or condition. However, if during the course of conducting clinical procedures, a participant is found to have a result outside of clinical norms, the participant will be contacted by the researcher either during a visit or over the phone to direct them to contact a medical provider for further evaluation. If a woman tests positive for pregnancy, the results will be shared with the participant, they will be withdrawn from the study, and they will be advised to follow up with their doctor for prenatal medical care.

13 Subject Payment and/or Travel Reimbursements

Participants will be compensated $40 for completing visit questionnaires and procedures, and $20 for completing the MRI scan. In addition, participants will receive a bonus of $20 for returning all e-cig supplies at Visit 4. The total possible compensation for completing all study procedures and returning study supplies is $220. Participants will be compensated via gift cards.

14 Economic Burden to Subjects

14.5 Costs

Participants will be provided with the study ECIG at no cost. Participants and/or insurance companies will not be responsible for costs related to study procedures and tests.

14.6 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is

available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15 Resources Available

15.5 Facilities and locations

The CNMRR building will be utilized for all in person participant visits. Penn State Health Zoom will be used for all remote visits.

15.6 Feasibility of recruiting the required number of subjects

In 2017, 18.7% of Pennsylvanian adults reported current cigarette smoking. With such a large proportion of smokers in the state, randomizing a total of 56 participants should be easily obtained.

15.7 PI Time devoted to conducting the research

Andrea Hobkirk, PhD will provide scientific leadership for the project including overall study administration, design, conduct, and publication and will be responsible for all communications with the Penn State IRB. She will train and supervise the PSU research staff and will ensure that study procedures are followed.

15.8 Availability of medical or psychological resources

All of our participants will be seen by appropriately trained research staff. Any serious AEs or concerning test results will be passed on to participants along with a letter to their doctor. Any urgent health problem will require accompanying the participant to the ER, which is located on the same campus as The Center for NMR Research.

15.9 Process for informing Study Team

Weekly team meetings to discuss study procedures, questions, and issues will be conducted with all members of the PSU research team. Prior to the study start, all team members will be trained on the protocol and standard operating procedures. In addition weekly meetings will be held to discuss study progress. Current study documents including the protocol, consent, and study measures are maintained on a shared drive to ensure that all study team members have access to the most current version of all study documents. Any modifications to the study and IRB-approvals are communicated via email or via the document sharing service.

16 Other Approvals

16.5 Other Approvals from External Entities

N/A

16.6 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☒ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17 Multi-Site Study

17.5 Other sites

N/A

17.6 Communication Plans

N/A

17.7 Data Submission and Security Plan

N/A

17.8 Subject Enrollment

N/A

17.9 Reporting of Adverse Events and New Information

N/A

17.10 Audit and Monitoring Plans

N/A

18 Adverse Event Reporting

18.5 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a 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 functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be 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.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research 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.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

18.6 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at study visits.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms

- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

18.7 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

18.8 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.8.1.1 Written IND/IDE Safety Reports

N/A

18.8.1.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions

N/A

18.9 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

18.10 Unblinding Procedures

If an adverse event requires that the participant be unblinded, the unblinded study personnel will be able to provide that information as needed. This will be reported appropriately along with the adverse event in accordance with the safety monitoring plan. Otherwise, participants will not be unblinded to their assigned study condition.

18.11 Stopping Rules

In the event of unexpected or serious adverse events that the principal investigator believes are related to ECIG use or study procedures, the IRB will be notified, and their recommendations will be followed.

19 Study Monitoring, Auditing and Inspecting

19.5 Study Monitoring Plan

19.5.1.1 Quality Assurance and Quality Control

Responsibility for data quality and study conduct lies with the Principal Investigator. Dr. Hobkirk will oversee that the study is executed in compliance with the protocol, IRB policies and Good Clinical Practice.

Data will be collected from participants and coded directly by either using the REDCap survey tool (participant entered data) or through REDCap data entry forms (researcher entered data). The codes that link the name of the participant and the study ID will be kept confidential in REDCap. Any paper forms (i.e., consent) will be securely transported to the PI's data entry center. Any additional data that is generated will be stored electronically on the PHS server in password protected files.

Study data will be managed using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g., for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (e.g., SPSS, SAS, Stata, R/S-Plus). The system was developed by a multi-institutional consortium which includes The Pennsylvania State University and was initiated at Vanderbilt University. The database is hosted at the Penn State Hershey Medical Center and College of Medicine data center, which will be used as a central location for data processing and management. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies.

REDCap is HIPAA compliant. Data are stored on a secure server; data in REDCap are encrypted; access to the database requires authentication (a unique username and password); data are accessed based on the individual's role on the project; every interaction with the data is logged, creating an audit trail.

Random data entry checks will be implemented regularly to identify problems with data entry. Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. In addition, electronic edit checks, and random internal quality and assurance checking will be performed manually. Data quality will be monitored by random inspection of the completed electronic forms by one of the research assistants and any problems detected will be discussed with the PI. If necessary, re-training of researchers will be conducted.

The responsibility for data quality and study conduct lies with the PI.

19.5.1.2 Safety Monitoring

Events will be reported using this timeline:

Class	Severity	Expectedness/Relatedness	Location	Reporting Timeline
1	Serious	- Unexpected - Related or possibly related	All	2 business days from occurrence
2	Non-serious	- Unexpected - Related or possibly related	All	Annual

3	Serious or non-serious	- Expected	All	Annual

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **research coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

20 Future Undetermined Research: Data and Specimen Banking

20.5 Data and/or specimens being stored

Urine samples will be stored with the participant's code number, date, and time.

20.6 Location of storage

Urine samples will be stored in the Penn State TCORS lab space on the 3rd floor of the Penn State Hershey Cancer Institute.

20.7 Duration of storage

Urine samples will be stored indefinitely.

20.8 Access to data and/or specimens

The principal investigator and study team members will have access to the samples.

20.9 Procedures to release data or specimens

Researchers wishing to utilize the stored samples should submit a request in writing to the principal investigator. The request should include a proposal for how the samples will be utilized. If approved, the principal investigator will develop a plan to provide the researcher with the samples. The samples will not contain any identifiable information. If requested, basic unidentifiable demographic information can be provided.

20.10 Process for returning results

Results should be provided to the principal investigator at the completion of analysis and prior to publication.

21 References

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22 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

See the Research Data Plan Review Form