



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

Protocol Title:

Provide the full title of the study as listed in item 1 on the “Basic Information” page in CATS IRB (<http://irb.psu.edu>).

Testing the Effect of ENDS Flavors on Neurotransmission

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Version Date:

Provide version date for this document. This date must be updated each time this document is submitted to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

November 14, 2024

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See “HRP-103- Investigator Manual,” under “ClinicalTrials.gov” for more information.

NCT05836051

Important Instructions for Using This Protocol Template:

This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.

1. GENERAL INSTRUCTIONS¹:

- Prior to completing this protocol, ensure that you are using the most recent version by verifying the protocol template version date in the footer of this document with the current version provided in the CATS IRB Library.
- Do not change the protocol template version date located in the footer of this document.
- Some of the items may not be applicable to all types of research. If an item is not applicable, please indicate as such or skip question(s) if indicated in any of the instructional text.
- **GRAY INSTRUCTIONAL BOXES:** Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.
 - **Do NOT delete the instructional boxes from the final version of the protocol.**
- The protocol should be written in lay language. Do **NOT** copy and paste grant proposal information into the protocol.
- Add the completed protocol template to your study in CATS IRB (<http://irb.psu.edu>) on the “Basic Information” page.

¹ This template satisfies AAHRPP elements 1.7.B, 1.8.B, 1-9, II.2. A, II.2.I, II.3.A, II.3.B, II.3.C-II.3.C.1, II.3.D-F, II.4.A, III.1.C-F, II.2.D

2. **CATS IRB LIBRARY:**

- Documents referenced in this protocol template (e.g. SOP's, Worksheets, Checklists, and Templates) can be accessed by clicking the Library link in CATS IRB (<http://irb.psu.edu>).

3. **PROTOCOL REVISIONS:**

- When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the guides available in the Help Center in CATS IRB (<http://irb.psu.edu>) for using track changes.
- Update the Version Date on page 1 each time this document is submitted to the IRB office with revisions.

If you need help...

All locations:

Human Research Protection Program

Office for Research Protections

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University Park, PA 16802-7014

Phone: 814-865-1775

Fax: 814-863-8699

Email: irb-orp@psu.edu

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1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

Study Purpose: The overarching goal of this translational proposal is to determine if neuroactive flavor chemicals can enhance the addiction potential of electronic nicotine delivery systems (ENDS) by altering brain function and behavior. This proposed study will be a close human translation of robust preclinical findings in mice showing that specific neuroactive green apple flavor chemicals alter brain dopamine transmission to enhance flavor-induced reward and reinforcement, while other neuro-inactive green apple flavor chemicals have no influence on dopamine transmission in the brain. This effect has not yet been confirmed in humans. If our hypotheses are supported, the study will provide clear evidence that specific flavor chemicals can have neuroactive effects beyond taste perception alone, since both chemicals produce a similar green apple taste. The findings will point to a specific neurobiological mechanism for the role of flavors in ENDS addiction potential.

Study overview: For this randomized double-blind controlled trial, adults who use ENDS will be randomized to use ENDS with an e-liquid containing a neuroactive flavor (hexyl acetate) vs. an inactive flavor (ethyl acetate) for ten days as a supplement to their typical tobacco use. Laboratory measures of ENDS reinforcement, subjective ENDS ratings, and brain reactivity to the flavor using functional magnetic resonance imaging (fMRI) will be collected at baseline and after ten days of ENDS use.

The primary aim is as follows:

Assess for the presence of cumulative flavor effects by comparing changes in ventral tegmental area (VTA) reactivity and absolute reinforcement to hexyl acetate vs. ethyl acetate from baseline to post-use.

Hypothesis: Compared to ethyl acetate, hexyl acetate will result in larger increases in VTA reactivity to the inhalation of ENDS flavor and absolute reinforcement measured by the number of ENDS puffs taken over the 10-day use period.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Research typically has a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

Study Endpoints:

Support for our hypotheses will be evidenced by a group difference in pre-to-post changes in brain reactivity and average puff number with small to medium effect sizes or larger ($\eta^2 > .03$) demonstrating larger increases for the hexyl acetate vs. ethyl acetate groups using analyses of variance. Given the large variability in human behavior and brain responses, it is reasonable to assume that the ratio of effect size to standard deviation (R) is in the range of 1.0 to 1.5. Based on our power analysis—conducted under the assumption of fixed effects analysis of variance with power of 80% and pre-specified Type I error probability of 0.05—we need 17 per group to detect small effects (R=1.0) and 12 per group to detect medium effects (R=1.25). With 30 in each group and within by between subjects effects, we should sufficiently powered to measure our primary study end-points and to conduct secondary analyses on task behavior.

1. VTA reactivity will be calculated as the percent change in average BOLD signal in a pre-defined VTA region of interest during inhalation of flavored vs. unflavored aerosol. VTA reactivity will be measured using functional MRI during a blocked puffing paradigm that will include the inhalation of ENDS aerosols that contain the assigned ENDS flavor and an unflavored control aerosol.
2. Absolute reinforcement will be calculated as the change in the average number of puffs per day during a 10-day use period from the first four-day average to the last four-day average. Ad-lib ENDS use at home will be measured objectively with topography equipment.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Not applicable

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the treatment, drug, or device is available to patient without taking part in the study.

As of 2019, 8.1 million adults and 3.5 million youth in the United States were current, regular, electronic nicotine delivery system (ENDS) users.^{1,2} The vast majority use ENDS with flavors other than tobacco, including approximately 97% of youth and young adults and 81% of older adults.³ The last two data collection waves of the Population Assessment of Tobacco and Health (PATH) study found that fruit flavors are by far the most popular among established ENDS users of all ages, with an estimated 70% of ENDS-using youth and adults using fruit-flavored ENDS in the last 30 days in 2015.^{4,5} Flavored ENDS are a public health concern for their role in ENDS initiation among young, never smokers.¹⁵ About 85% of youth initiate ENDS use with flavored products and their most prevalent self-reported reason for using ENDS is because they “come in flavors I like”.¹⁵ Although it is clear that flavors contribute to ENDS initiation, it is not yet fully understood if flavors influence use escalation and the risk of becoming addicted to ENDS. The impact of flavors on use and addiction is increasingly important as new flavored ENDS products continue to reach the market.

Conclusions about the addictive potential of flavored ENDS has been limited by conflicting observational trends in use frequency and duration. Population-based surveys provide some evidence that flavors are associated with higher frequency of ENDS use, but do not consistently show that flavors result in longer duration of use, which is an essential marker of dependence.¹⁶⁻¹⁸ For example, a school-based survey found that students using ENDS with non-traditional flavors were almost 4 times more likely to continue using ENDS over the next 6 months compared to those using traditional flavors (e.g., tobacco, menthol).¹⁸ However, a separate school-based survey found that, after accounting for cigarette smoking, using ENDS for their flavors was not a significant predictor of continued use after 6-months.¹⁷ Among adults, current and former cigarette smokers often transition from tobacco to fruity and dessert flavored products over time, suggesting that flavors might help to maintain long-term ENDS use.^{19,20} One significant limitation of this research is the lack of a neurobiological mechanism to explain use and the assumption that flavors within the same profile (i.e., they taste the same) should have a similar effect on

use behaviors and addiction potential. We are proposing that the specific flavor chemicals, not taste, determine long-term use behaviors and addictive potential.

Several clinical experimental studies with humans have shown evidence that the acute administration of sweet flavors may enhance the appeal, reward, and reinforcement of ENDS.^{10,11,21} However, this behavioral research has also been inconsistent and inconclusive and has not investigated the effects of chronic flavored ENDS use. In a study of smokers with some ENDS use experience, flavored ENDS containing nicotine were related to higher subjective liking ratings, higher motivation to work for puffs on a computerized task, and more ad-libitum use compared to unflavored ENDS containing nicotine.²¹ Other studies with ENDS users found that sweetened ENDS were associated with more self-reported appeal, willingness to use again, and willingness to pay for ENDS than unsweetened or unflavored ENDS, regardless of nicotine concentration.^{10,11} Sweet flavors have also been linked to higher puff volume during ENDS use.²² However, the findings from experimental studies have been inconsistent. Although sweet flavors were related to increase ENDS puff volume, they were not associated with more puffs, a primary contributor to the development of addiction.²² A recent experimental study found that green-apple flavored ENDS did not satisfy cigarette craving among smokers as much as menthol flavored ENDS and had no effect on craving, cognitive performance, or physiological arousal over the dose of IV administered nicotine.²³ In line with the rationale that taste dictates ENDS reward, the currently published studies rarely provide information about specific flavor chemicals in the e-liquid, only the resulting flavor profile. In addition, participants in these studies only used the flavored ENDS during the experiment without chronic use periods to allow for the development of cumulative effects on behavior. Our preliminary research shows that the specific flavor chemicals used and the cumulative effects of these chemicals on the brain over time are vitally important to their role in ENDS reward and reinforcement.⁹

The ventral tegmental area (VTA) is arguably the most critical brain region in drug addiction for its central role in reward and reinforcement.^{24,25} Nearly all drugs of abuse, including nicotine, stimulate the VTA that causes a cascade of dopamine release from the nucleus accumbens projecting to the prefrontal cortex.^{24,25} This series of activation along the mesolimbic pathway is the driving mechanism behind reward and reinforcement. Thus, the degree to which a drug stimulates the VTA is an objective marker of how rewarding, reinforcing, and ultimately, how addictive the drug is likely to be. The oral ingestion of non-caloric flavors does not elicit strong activation of the VTA.²⁶ However, unlike flavored foods and beverages, ENDS flavors are inhaled, which provides a direct route to the VTA via the bloodstream.

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Flavor additives in ENDS become aerosolized in the e-liquid and inhaled along with nicotine and other chemical constituents.²⁷ The U.S. Food and Drug Administration found that almost all flavor compounds in e-liquids are lipophilic and smaller than the blood-brain-barrier threshold (400 kilodaltons).⁷ This means that flavor compounds in the bloodstream can freely enter the brain. The FDA used computational analysis to confirm that the structures of flavor compounds are similar to naturally-occurring neuroactive compounds, suggesting a high potential for flavors to bind to receptors in the brain causing psychoactive effects and the potential for neurotoxicity.⁷ Recent preclinical research conducted by our team adds further evidence of flavors' direct effects on the brain by demonstrating that specific fruit and menthol flavor chemicals can alter ENDS reward by modulating VTA dopamine transmission through direct or indirect actions on nicotinic acetylcholine receptors (nAChRs) in the midbrain.⁹ We conducted several studies using conditioned place preference tasks in mice genetically modified to contain fluorescent nAChRs.^{13,28,29} Conditioned place preference (CPP) is a non-contingent reward-related assay used commonly in rodent models. Paired with these assays, we used fluorescence microscopy and electrophysiology to examine the effects of specific green-apple and menthol flavor chemicals on nAChR stoichiometry, upregulation, and VTA dopamine firing frequency. These studies showed that specific green-apple flavorants (i.e., hexyl acetate, farnesene, farnesol) upregulate nAChRs

on VTA dopaminergic neurons, increase VTA firing frequencies and elicit reward-related behavior independent of nicotine.^{13,30} These effects may be sex-dependent since the green apple flavorant farnesol produced reward related behavior only in male mice, but farnesene produced reward-related behavior in both male and female mice.^{13,30} Interestingly, these experiments demonstrated flavor-induced VTA effects even though the flavor was delivered via intraperitoneal injections that bypassed taste perception. The findings were confirmed by a novel vapor self-administration paradigm that facilitated a contingent vapor delivery of nicotine and/or flavorants to examine reinforcement-related behavior in mice.¹⁴ A series of studies support that the green-apple flavor hexyl acetate has profound effects on nAChR activity and use behaviors whereas other green-apple flavors, such as ethyl acetate, do not, despite both having a similar taste. The vaping administration paradigm was designed to generalize to human ENDS use and is the inspiration for the current translational study design. It is described in more detail in the preliminary research section.

2.2 Previous Data

Describe any relevant preliminary data.

Our robust preclinical research from these rigorous mice experiments provides strong evidence for VTA activity as the primary mechanism driving reward and reinforcement of common ENDS flavor chemicals, such as hexyl acetate, even when taste perception is bypassed.^{13,14,30} To our knowledge, only three studies have investigated the acute or chronic effects of ENDS aerosols on brain function for humans. Wall and colleagues were the first to show that tobacco-flavored ENDS elicited acute brain activation throughout mesolimbic and cortical brain regions using fMRI among 10 daily smokers, but did not assess flavor effects.³¹ Kroemer and colleagues used fMRI to show that, after using four different ENDS for 2-days each, smokers had stronger reactivity in the nucleus accumbens to visual cues of ENDS that were sweetened compared to unsweetened and contained nicotine vs. no nicotine.¹² This study was focused on sweet taste profiles and the development of learned conditioned cues, not specific flavor chemicals or acute administration. Our group developed MRI-compatible ENDS aerosol delivery equipment to compare the acute neural effects of inhaling strawberry-vanilla and unflavored aerosols containing a low dose of nicotine during fMRI with nine female daily smokers.³² In contrast to our hypothesis, we found that our sweet-flavored aerosol only activated the primary gustatory cortex, not the VTA. This finding helped to inform our current rationale that ENDS flavors do not show strong acute effects on the VTA and may have no effect at all if inactive flavor chemicals are used.

2.3 Study Rationale

Provide the scientific rationale for the research.

For the proposed study, we will control for taste perception and the development of conditioned taste-nicotine cues to isolate the cumulative direct effects of flavor chemicals on VTA activity. If our hypotheses are supported, the proposed study along with our preclinical mechanistic research will provide substantial evidence that specific flavor chemicals have direct effects on dopaminergic brain regions that influence reward and escalation to addiction. This will provide a clear neurobiological mechanism of flavored ENDS to prevent and treat addiction.

In summary, the scientific rationale for the proposed study is supported by rigorous preclinical research showing direct neuroactive effects of specific flavor chemicals that enhance reward and reinforcement. Our proposed study is designed to primarily answer one simple, but important question: Do specific flavor chemicals affect neurobehavioral processes relevant to addiction through direct neural mechanisms beyond taste perception? If the answer to this question is yes, it will challenge our current

understanding of the role of flavors in ENDS addiction potential and will guide new, specific investigations of the neuroactive properties and health effects of inhaled flavor chemicals.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children** –Review “HRP-416- Checklist - Children”
- **Pregnant Women** – Review “HRP-412- Checklist - Pregnant Women”
- **Cognitively Impaired Adults**- Review “HRP-417- Checklist - Cognitively Impaired Adults”
- **Prisoners**- Review “HRP-415- Checklist - Prisoners”
- **Neonates of uncertain viability or non-viable neonates**- Review “HRP-413- Checklist - Non-Viable Neonates” or “HRP-414- Checklist - Neonates of Uncertain Viability”

[Do not type here]

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.).

1. 21 to 60 years old
2. Regular users of electronic nicotine delivery systems (e.g., e-cigarettes and vapes) on ≥ 5 days out of the last 28.
3. Not planning to quit tobacco use within next month
4. Able to read and write in English

3.1.1 Does this research involve collecting data from individuals residing outside of the US?

☒

No

☐

Yes – identify the countries where data collection will take place

[Type protocol text here]

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

1. Major neurological conditions or brain trauma
2. Current substance use impairing participation
3. Unstable or significant medical conditions (e.g., COPD, coronary heart disease)
4. Current use of smoking cessation medication (e.g., varenicline, patch)

5. Uncontrolled serious mental illness, suicidality, or inpatient psychiatric hospitalization in the past 6 months
7. Known allergic reaction to ENDS liquids ingredients propylene glycol or vegetable glycerin
10. Unable to use study provided ENDS ad-libitum for at least 3 hours per day
12. Pregnant or breastfeeding as indicated by self-report or urine pregnancy screen

MRI specific exclusions:

1. MRI safety contraindications (e.g., metal implants, claustrophobia)
2. Major neurological conditions or brain trauma

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

- Participants may choose to remove themselves from the study by informing the research team at any point during the study.
- Participant doesn't comply with the protocol, behaves in an inappropriate or threatening manner, or admits to providing inaccurate eligibility criteria.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; the follow-up for subjects withdrawn from investigational treatment.

Not applicable

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (<http://irb.psu.edu>). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (<http://studyfinder.psu.edu>) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (<http://irb.psu.edu>).

[Do not type here]

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (<http://studyfinder.psu.edu>) for recruitment purposes, include this method in this section.

- Information provided in this protocol, including the description of study procedures, compensation, and recruitment, needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For research utilizing **Penn State Health patient data**, please note the following:

- Submissions using **Enterprise Information Management (EIM)** for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form in CATS IRB (<http://irb.psu.edu>). See “HRP-103- Investigator Manual, Study Recruitment” for additional information.
- Direct contact with patients for research recruitment that does not occur in person will require review of the contact list by Penn State Health’s contracted mail company, **Allegra**. See the following for additional information: <https://pennstatehealth.sharepoint.com/COM-IT%20Resources/SitePages/Data%20&%20Analytic%20Services.aspx> (Penn State Health ePass login required).

Recruitment for this study will be facilitated through IRB STUDY00002213 (Study name: Call Routing Screener) which will serve as the initial recruitment point of contact. We will also use StudyFinder, word of mouth, and flyers in the community to identify participants. STUDY00002213 includes all recruitment materials, including participant letters/emails and phone/text message scripts.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate ‘not applicable’ if subjects will not be prospectively recruited to participate in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.).

If applicable, state whether the study team will access medical records before or after engaging the potential subject.

DO NOT include the actual recruitment material or wording in this protocol.

[Do not type here]

4.2.1 How potential subjects will be recruited.

Subjects will be recruited via IRB STUDY000002213, StudyFinder, word of mouth, and flyers in the community. Subjects from Study 2213 will be contacted via phone, mail, or email. Subjects from StudyFinder will be contacted via the preferred contact method they indicated on the form. All subjects will identify themselves as a possible subject by contacting the study team after interacting with any of the above methods.

4.2.2 Where potential subjects will be recruited.

Recruitment will occur over the phone and through an automated online preliminary eligibility survey.

4.2.3 When potential subjects will be recruited.

While enrollment is open the study will be continuously recruiting subjects until the target number of completed subjects is reached.

4.2.4 Screening and determining eligibility

Screening involves the process of assessing whether or not a potential subject is eligible for a study based on the inclusion and exclusion criteria. This process only involves assessing the eligibility and collecting information/data/biospecimens that is not related to eligibility does not meet the definition of screening and requires prior written consent.

There are some specific situations in which consent is not required prior to screening activities, and otherwise, consent is required prior to screening. Answer the following items in order to describe the screening process and determine if prior consent is required.

4.2.4.1 For the purpose of screening/determining eligibility, is the potential subject providing information through oral or written communication (e.g. survey or verbally responding to answers)?

☒ Yes

If on phone: After being read the Summary Explanation of Research and providing verbal consent to the screening assessment, participants will be asked questions about the inclusion and exclusion criteria as well as their identifying information, including name and preferred contact methods.

If done through online version of phone screen: After reading the Summary Explanation of Research and providing implied consent to the screening assessment, participants will answer questions about the inclusion and exclusion criteria as well as their identifying information, including name and preferred contact methods.

☐ No

4.2.4.2 Is eligibility being determined by obtaining identifiable private information or biospecimens by accessing records or stored identifiable biospecimens?

☐ Yes [NOTE: HIPAA authorization or a waiver of HIPAA authorization may be necessary – see section 6.0]

[Describe what is being accessed here]

☒ No

4.2.4.3 Is the potential subject being asked to do any activity for screening and eligibility purposes beyond what is described above (e.g. fast, blood test)?

☐ Yes [NOTE: consent process or waiver of consent is required – see section 5.0]

[Describe the activity here]

☒ No

4.2.4.4 Is the screening data to be used for purposes other than eligibility or recruitment (e.g. retained for data analysis or for other purposes)?

☒ Yes [NOTE: consent process or waiver of consent is required – see section 5.0]

[Eligibility information will be retained in our secure REDCap database to be included in study trial CONSORT diagrams. Since we are retaining this information even for ineligible participants, we are collecting verbal and/or implied consent prior to all screening procedures.]

☐ No

5.0 Consent Process and Documentation

Refer to the following materials:

- The “HRP-090- SOP - Informed Consent Process for Research” outlines the process for obtaining informed consent.
- The “HRP-091– SOP - Written Documentation of Consent” describes how the consent process will be documented.
- The “HRP-314- Worksheet - Criteria for Approval” section 7 lists the required elements of consent.
- The “HRP-312- Worksheet - Exemption Determination” includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (<http://irb.psu.edu>). Links to Penn State’s consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

[Do not type here]

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; If this is the only box checked, mark Sections 5.3, 5.4 and 5.5 as ‘Not applicable’]
- ☒ **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; If this is the only box checked, mark Sections 5.4 and 5.5 as ‘Not applicable’]
- ☐ **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; If this is the only box checked, mark Section 5.5 as ‘Not applicable’]
- ☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement.** [Complete Section 5.5; If this is the only box checked, mark Sections 5.2, 5.3, 5.4 and 5.6 as ‘Not applicable’]

5.2 Obtaining Informed Consent

5.2.1 Consent Process

Describe the consent process (when, where, and how), including how subjects indicate consent. If there are multiple consent processes, describe each process separately.

Before collecting information during the preliminary eligibility survey, participants will provide verbal consent (phone) or implied consent (online) after reading a summary explanation of benefits by study personnel and given a chance to ask questions. At the in-person laboratory visit, subjects will provide written informed consent for all study procedures. Subjects will be offered to have an electronic version of the written consent form emailed or a paper copy mailed to them prior to the visit. Subjects will be given a paper copy of the written consent form at the beginning of their in-person study visit in the Penn State MRI Center.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

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 trial participation is voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not.

5.3 Waiver of Written Documentation of Consent

Review “HRP – 411 – Checklist – Waiver of Written Documentation of Consent.”

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

- ☒ The research presents no more than 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.)*

For distinct cultural groups describe the alternative mechanism for documenting that informed consent was obtained:

This waiver of written consent documentation is being requested to allow the pre-screen procedures to take place. No PHI will be gathered prior to interaction with participants.

Information collected during the screening process will be included in the study regardless of participant's eligibility for the construction of Consort Diagrams.

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, or implied consent form)

A HRP-585 will be read/presented to subjects prior to the completion of the study screening form. Participants will be given a written or electronic copy of the full consent form prior to or at the study visit based on their preference.

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

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

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

Not applicable

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

Not applicable

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

Not applicable

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

Not applicable

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

Not applicable

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Not applicable

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

Review “HRP-410-Checklist -Waiver or Alteration of Consent Process” to ensure that you have provided sufficient information.

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

Not applicable

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

Not applicable

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

Not applicable

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

Not applicable

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation.

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review “HRP-091 –SOP- Written Documentation of Consent” and “HRP-103 -Investigator Manual” to ensure that you have provided sufficient information.

Non-English speaking subjects will not be enrolled in this study because the surveys and computer tasks used in the procedures have not been translated to other languages.

5.6.2 Cognitively Impaired Adults

Refer “HRP-417 -CHECKLIST- Cognitively Impaired Adults” for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual’s authority to consent to research.

For research conducted in the state of Pennsylvania, review “HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians” to be aware of which individuals in the state of Pennsylvania meet the definition of “legally authorized representative.”

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of “children” in “HRP-013 -SOP- Legally Authorized Representatives, Children, and Guardians.”

Not applicable

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some, or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual’s authority to consent to each child’s general medical care.

For research conducted in the state of Pennsylvania, review “HRP-013-SOP- Legally Authorized Representatives, Children and Guardians” to be aware of which individuals in the state of Pennsylvania meet the definition of “children.”

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of “children” in “HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians.”

Not applicable

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable

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

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See “HRP-103 -Investigator Manual” for a list of the 18 identifiers.

[Do not type here]

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]*
- ☒ **Signed authorization will be obtained and documented.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*
- ☒ **Partial waiver for recruitment purposes only (e.g., 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 for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

- ☒ **Alteration to waive requirement for written documentation of authorization (verbal or implied authorization).** [Complete all parts of sections 6.2 and 6.3]

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

This section is about the disclosure of PHI as it relates to the requested authorization waiver and/or alteration. Complete each item in this section in relation to each requested waiver of authorization and/or alteration (the last three boxes in Item #6.1). For example, if requesting a partial waiver for recruitment, these items need to address the PHI for recruitment rather than addressing the use of PHI for the entire study.

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

Include the following statement as written – DO NOT ALTER **If the research does not involve a waiver or alteration of authorization, remove the statement and indicate as not applicable.**

Information is included in the “Confidentiality, Privacy and Data Management” section of this protocol or in “HRP-598 – Research Data Plan Review Form”.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers (associated with the waiver and/or alteration of authorization) at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed.

If identifiers are to be retained, provide the legal, health or research justification for retaining the identifiers.

For this clinical trial we will retain identifiers to assess for potential bias in our final sample based on reasons for ineligibility among those screened. For this process we will need identifiers to determine if any individuals were screened multiple times.

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

Provide reasons why this research could not practicably be carried out without access to and use of PHI (that is requested in the waiver and/or related to the alteration of authorization).

PHI is necessary to determine if people are safe to participate in the study procedures.

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

Provide reasons why this research could not practicably be carried out without the waiver and/or alteration of authorization. If more than one waiver and/or alteration of authorization (e.g., waiver for recruitment and alteration for verbal authorization) is requested, make sure to provide reasoning for each request.

Collecting informed consent prior to eligibility screening is not feasible because it would place unnecessary burden on interested volunteers who are not eligible for participation and on study staff who would spend time collecting informed consent and compensating a large number of ineligible participants.

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER. **If the research does not involve a waiver or alteration of authorization, remove the statement and indicate as not applicable.**

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

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (<http://irb.psu.edu>). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions).

[Do not type here]

7.1 Study Design

Describe and explain the study design.

For this randomized double-blind controlled trial, regular ENDS users will be randomized to use ENDS with an e-liquid containing a neuroactive sweet flavor (hexyl acetate) vs. an inactive sweet flavor (ethyl acetate) for ten days as a supplement to their typical tobacco use. Laboratory measures of ENDS reinforcement, subjective ENDS ratings, and brain reactivity to the flavor using functional magnetic resonance imaging (fMRI) will be collected at baseline and after ten days of ENDS use. The ENDS will contain nicotine and we expect to complete 25 participants in each group (1:1) (Figure 1).

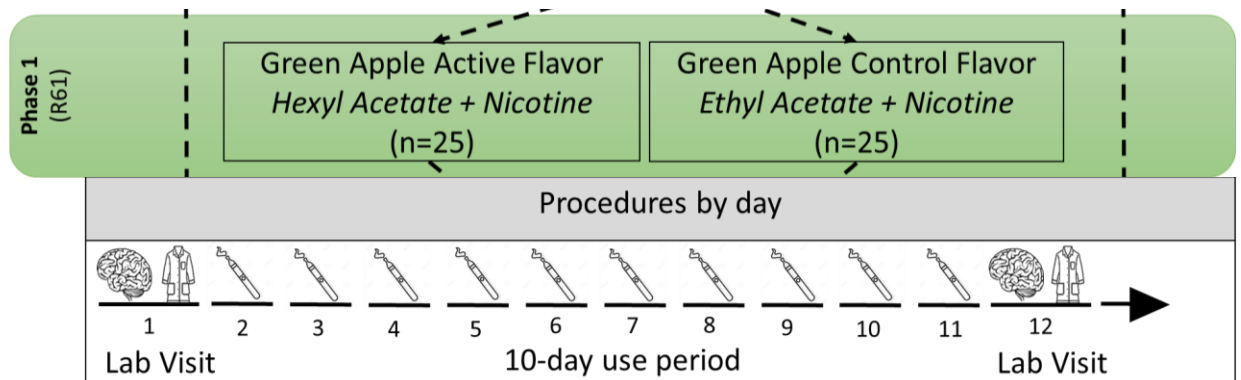


Figure 1. Illustration of double-blind randomized controlled trial where 50 participants will be assigned to receive an e-cigarette that contains an e-liquid with hexyl acetate or ethyl acetate flavoring along with a low dose of nicotine. Participants will complete a laboratory visit that includes fMRI and reward tasks before and after using the assigned e-cigarette at-home for ten days.

7.2 Study Procedures

Provide a step-by-step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- **HOW:** (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.) For surveys, indicate if subjects are able to skip questions that they don't want to answer.
- **WHERE:** (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

All subjects will be asked to abstain from using nicotine in any form (smoking, vaping, etc.) for 14 hours prior to their study visit laboratory/MRI visits.

All subjects will complete the two laboratory visits. A subset of subjects who are able to complete the MRI will complete the MRI on the same day prior to their laboratory visit.

7.2.1 Initial Screener

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

- Possible subjects (identified as described in Section 4) will be contacted via email, text message or phone. Subjects contacted via email and/or text messaging will be given a link for the Initial Screener (uploaded to CATS) in REDCap. Subjects wishing to be contacted via phone will answer the questions on the Initial Screener verbally with a study team member.
- Subjects who meet preliminary eligibility criteria based on the Initial Screener will be scheduled for a Remote Screening Visit.

7.2.2 Remote Screening Visit

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

- This visit will be conducted via Penn State Health Teams or over the phone.
- The following information will be collected to determine eligibility and collect baseline information:
 - REDCap Survey Questionnaires:
 - Current and past history of tobacco use
 - Tobacco use dependence
 - Demographics
 - Alcohol use
 - Mood and anxiety symptoms
 - Chronic Obstructive Pulmonary Disorder
 - Adapted Questionnaire of Smoking Urges
 - Interview
 - Study eligibility screener
 - Medical history and concomitant medications
 - NIDA Substance use quick screen
 - MRI Safety Questionnaire
- Subjects who are eligible at this point will be scheduled for an in-person Pre-Randomization Laboratory Visit. Participants interested and eligible to complete MRI will also be scheduled for a Pre-Randomization MRI scan. They will be reminded to abstain from using any nicotine for 14 hours prior to their visit to the MRI Center

7.2.3 Pre-Randomization Visit

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

- This visit will be conducted in the Penn State MRI Center.
- All subjects will complete the laboratory visit portion. If able and willing, subjects will complete the Pre-Randomization MRI in addition to the laboratory visit. If the MRI scanner is not functional, functional near infrared spectroscopy imaging will be used instead.
- Pre-Randomization Laboratory Visit Procedures (all subjects)
 - Complete Written Consent form
 - Review all study procedures and safety information using participant guide (uploaded in CATS).
 - Exhaled Breath Carbon Monoxide measurement to assess for smoking abstinence using hand-held monitor
 - Urine collection for cotinine analysis and pregnancy determination (Obtain urine and process pregnancy test for women of child bearing age (have had a period in the past 12 months) who have not had a hysterectomy.)

- Hands-on training on how to use and store ENDS device.
 - Subjective ratings during puffing protocol
 - Participants will be asked to puff on four ENDS labeled A, B, and C corresponding to varying flavor combinations blinded to the participant. A, B, and C are labeled as such for simplicity in subject instruction. The ENDS will contain different concentrations of flavorants (hexyl acetate, ethyl acetate, methylbutyl acetate, ethyl maltol), base constituents (vegetable glycerin, propylene glycol), and 25 mg/ml nicotine concentration. Participants will be asked to provide subjective ratings of the ENDS (e.g., intensity, familiarity, sweetness, liking, satisfaction, similarity, etc.). For the primary outcome of subjective reward ratings, we will use a modified version of the Drug Effects Questionnaire (DEQ)^{51,52} that has been used previously to assess flavored ENDS liking with adolescents and young adults.⁵³
 - RRV Computer Task
 - Participants will complete a computerized relative reinforcing value task (RRVT_Screenshots uploaded to CATS) to determine how reinforcing flavored ENDS are compared to unflavored ENDS. This task has been used previously to demonstrate that flavor enhances the reinforcing value of ENDS containing nicotine.²¹ Participants will be asked to perform “work” by moving a computer mouse to hit targets on two computer screens to earn points toward puffs of the flavored or unflavored ENDS. The target pictures will be labels of the words flavored or unflavored. Participants will be instructed that they can switch between the computer screens (targets) as often as they would like throughout the task.
 - Survey battery as seen in Table 1
- Pre-Randomization MRI Procedures (Optional MRI subject only)
 - MRI Safety Questionnaire
 - A high-resolution T1 anatomical scan will be collected prior to the functional sequences.
 - MRI Aerosol Delivery Protocol
 - Prior to lying in the scanner, a respiration sensor is placed around their chest and the MEADS device tubing will be placed near their mouth. Participants will be asked to lie down in the MRI scanner and breathe at a natural pace. The aerosol will be delivered via the device tubing orally for 6 blocks. A standardized MRI-compatible olfactometer at the Penn State CNMRR will be used to deliver aerosols inside the scanner at the opening of the participant’s mouth through plastic Teflon tubing. Similar to the assigned ENDS, the aerosols used during scanning will contain a combination of flavorants (hexyl acetate, ethyl acetate, methylbutyl acetate, ethyl maltol), base constituents (vegetable glycerin, propylene glycol), and 15 mg/ml nicotine concentration.
 - Monetary Incentive Delay Task
 - The Monetary Incentive Delay Task (MID) is a well-validated task used to measure reward-based decision making during fMRI. In each trial, participants are presented with one of five stimuli. The stimuli include the Win Small (\$0.20), Win Big (\$5.00), Don’t Lose Small (\$0.20), Don’t Lose Big (\$5.00) and Neutral (no money at stake). The win stimuli are presented as circles, the lose stimuli are

presented as squares and the neutral stimulus is presented as a triangle. Following the presentation of one initial stimuli, a plus sign will appear on the screen, after the plus sign a black shape that is the same shape as the one the participant saw before the plus sign will appear on the screen. The participant is expected to press a button under their pointer finger as soon as they see the black shape. If they press too soon, too slow or they do not press when the black shape appears, they will not receive the outcome for that shape. The participants will complete 15 practice rounds before entering the fMRI scanner where they will complete 102 rounds of the MID task. Functional Near Infrared Spectroscopy (fNIRS)

- If participants are unable to complete an MRI scan for any reason (e.g., equipment issues, participant preference, or MRI contraindications), but would like to participate in the neuroimaging portion of the study, we will complete the same MRI tasks during recording with fNIRS.
- The NIRx NIRScout system will be used for fNIRS data collection. fNIRS is a non-invasive data collection method that uses infrared light sources and detectors to measure blood oxygenation and deoxygenation approximately 1.5 cm deep into the cortex of the brain. Participants' heads will be measured to aid in the selection of the correct cap size. Participants will then be fit with a cloth cap that contains plastic optodes (light sources and sensors) that make contact with the participant's scalp. This system uses light to assess changes in neural activity, unlike other neuroimaging techniques that use magnets or electrical potentials. There are no known risks of fNIRS imaging. Participants will sit in a chair alongside the fNIRS equipment for data collection (similar to EEG) and will complete the same tasks as described for the MRI scanner.

Table 1: Study Procedures Table

	Remote Screening	Pre-Randomization Visit	10-day at-home ENDS use	Post-Randomization Visit
Visit	1	2		3
Day	n/a	0	1-10	10
QUESTIONNAIRES				
Visit Screener	X			
Tobacco Use History	X			
Name Registry	X			
MRI Safety Form (if applicable)	X	X		X
Biomeasures		X		x
Demographics	X			
Medical History	X			
Concomitant Medications	X	X	X	X
Adverse Event Assessment		X		X
Daily myCap Survey			X	
Cigarette/E-cigarette Details	X			

Alcohol Audit-C	X			
NIDA Quick Screen	X			
COPD	X			
Snaith-Hamilton Pleasure Scale (SHAPS)	X			
Temporal Experience of Pleasure Scale (TEPS)	X	X		X
Perceived Stress Scale (PSS)	X	X		X
Kessler K6	X	X		X
Cigarette Dependence (Fagerstrom and Penn State Cigarette Dependence Index)	X			
PATH TDI Dependence Cigarette	X			
Penn State Electronic Cigarette Dependence Index	X			
PROMIS Dependence Cigarette	X			
PATH TDI Dependence E-Cigarette	X			
PROMIS Dependence E-Cigarette	X			
DSM Dependence Cigarette	X			
Minnesota Withdrawal Scale		X		X
Craving		X		X
Questions on Smoking Urges (Q	X	X		X
Cigarette liking scale		X		X
Modified E-Cigarette Evaluation Questionnaire (MECEQ)		X		X
Labeled Hedonic Scale (LHS)		X		X
Drug Effects Questions (DEQ)		X		X
Taste Ratings		X		X
PROCEDURES				
Subjective ENDS Ratings		X		X
RRVT Computer Task		X		X
fMRI Tasks during neuroimaging (if applicable)		X		X
BIOMEASURES				
Urine Pregnancy Test		X		X
Exhaled CO		X		X
Urine Cotinine Collection		X		X

7.2.4 At-Home ENDS Use Surveys

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

- Participants will be instructed to use their ENDS at least 10 time per day. Participants will be told that they can continue using their regular nicotine product as often as they would like, but will be encouraged to replace their regular use with the assigned ENDS to avoid more nicotine exposure than usual during the study period. Participants will receive added information on the symptoms of nicotine toxicity (e.g. nausea, dizziness) and nicotine addiction (e.g., increased craving and irritability when not using) and will be advised to stop product use if they experience any of these symptoms and to notify the research team.
- Using the myRedCap systems and the myCap application, subjects will be sent an at-home ENDS Use survey in the evening on each day starting on their Pre-Randomization

Visit day and ending on the evening prior to their Post-Randomization Visit day. Participants will also receive a paper version of the log.

7.2.5 Post-Randomization Visit

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

- This visit will be conducted in the Penn State MRI Center.
- All subjects will complete the laboratory visit portion. If able and willing, subjects will complete the Post-Randomization MRI in addition to the laboratory visit portion.
- Post-Randomization Laboratory Visit Procedures (all subjects)
 - Exhaled Breath Carbon Monoxide measurement to assess smoking abstinence using hand-held monitor
 - Urine collection for cotinine analysis and pregnancy screen if indicated.
 - Subjective ratings during puffing protocol
 - Participants will be asked to puff on four ENDS labeled A, B, and C corresponding to varying flavor combinations blinded to the participant. A, B, and C are labeled as such for simplicity in subject instruction. The ENDS will contain different concentrations of flavorants (hexyl acetate, ethyl acetate, methylbutyl acetate, ethyl maltol), base constituents (vegetable glycerin, propylene glycol), and 25 mg/ml nicotine concentration. Participants will be asked to provide subjective ratings of the ENDS (e.g., intensity, familiarity, sweetness, liking, satisfaction, similarity, etc.). For the primary outcome of subjective reward ratings, we will use a modified version of the Drug Effects Questionnaire (DEQ)^{51,52} that has been used previously to assess flavored ENDS liking with adolescents and young adults.⁵³
 - RRV T Computer Task
 - Participants will complete a computerized relative reinforcing value task (RRVT_Screenshots uploaded to CATS) to determine how reinforcing flavored ENDS are compared to unflavored ENDS. This task has been used previously to demonstrate that flavor enhances the reinforcing value of ENDS containing nicotine.²¹ Participants will be asked to perform “work” by moving a computer mouse to hit targets on two computer screens to earn points toward puffs of the flavored or unflavored ENDS. The target pictures will be labels of the words flavored or unflavored. Participants will be instructed that they can switch between the computer screens (targets) as often as they would like throughout the task.
 - Survey battery as seen in Table 1
- Post-Randomization MRI Procedures (Optional MRI subject only)
 - MRI Safety Questionnaire
 - A high-resolution T1 anatomical scan will be collected prior to the functional sequences.

- MRI Aerosol Delivery Protocol
 - Prior to lying in the scanner, a respiration sensor is placed around their chest and the MEADS device tubing will be placed near their mouth. Participants will be asked to lie down in the MRI scanner and breathe at a natural pace. The aerosol will be delivered via the device tubing orally for 6 blocks. A standardized MRI-compatible olfactometer at the Penn State CNMRR will be used to deliver aerosols inside the scanner at the opening of the participant's mouth through plastic Teflon tubing. Similar to the assigned ENDS, the aerosols used during scanning will contain a combination of flavorants (hexyl acetate, ethyl acetate, methylbutyl acetate, ethyl maltol), base constituents (vegetable glycerin, propylene glycol), and 15 mg/ml nicotine concentration.
- Monetary Incentive Delay Task
 - The Monetary Incentive Delay Task (MID) is a well-validated task used to measure reward-based decision making during fMRI. In each trial, participants are presented with one of five stimuli. The stimuli include the Win Small (\$0.20), Win Big (\$5.00), Don't Lose Small (\$0.20), Don't Lose Big (\$5.00) and Neutral (no money at stake). The win stimuli are presented as circles, the lose stimuli are presented as squares and the neutral stimulus is presented as a triangle. Following the presentation of one initial stimuli, a plus sign will appear on the screen, after the plus sign a black shape that is the same shape as the one the participant saw before the plus sign will appear on the screen. The participant is expected to press a button under their pointer finger as soon as they see the black shape. If they press too soon, too slow or they do not press when the black shape appears, they will not receive the outcome for that shape. The participants will complete 15 practice rounds before entering the fMRI scanner where they will complete 102 rounds of the MID task.
- Functional Near Infrared Spectroscopy (fNIRS)
 - If participants are unable to complete an MRI scan for any reason (e.g., equipment issues, participant preference, or MRI contraindications), but would like to participate in the neuroimaging portion of the study, we will complete the same MRI tasks during recording with fNIRS.
 - The NIRx NIRScout system will be used for fNIRS data collection. fNIRS is a non-invasive data collection method that uses infrared light sources and detectors to measure blood oxygenation and deoxygenation approximately 1.5 cm deep into the cortex of the brain. Participants' heads will be measured to aid in the selection of the correct cap size. Participants will then be fit with a cloth cap that contains plastic optodes (light sources and sensors) that make contact with the participant's scalp. This system uses light to assess changes in neural activity, unlike other neuroimaging techniques that use magnets or electrical potentials. There are no known risks of fNIRS imaging. Participants will sit in a chair alongside the fNIRS equipment for data collection (similar to EEG) and will complete the same tasks as described for the MRI scanner.
 -

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Ideally, subjects will be in the study for a period of 11 days from the start of their pre-randomization visit to the completion of their post-randomization visit. Each in-person study visit can last up to three hours if MRI scanning is included. The remote visit will last two hours. Completing at-home survey logs will take approximately 5-minutes. For all study procedures, total participation time is expected to be up to 10 hours.

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

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics) used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

The UWELL Caliburn X pod-system will be used for all ENDS study procedures. This ENDS is made up of 2 parts, a battery and a cartomizer. The cartomizer contains the heating element and the liquid. The e-liquids will contain a combination of salt-formula nicotine, propylene glycol, vegetable glycerin, hexyl acetate, ethyl acetate, methylbutyl acetate, and ethyl maltol. Participants will be provided with 25 mg/ml nicotine e-liquid for use at home and during the laboratory visit. Aerosol delivered during the MRI scan will include 15 mg/ml nicotine. The cartomizers will be filled with liquid by the researchers and participants will be asked to bring the cartomizers (used and unused) to the researchers at the completion of the study to be weighed. Participants will be given the option to keep the ENDS and cartomizers at the end of the study.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

Participants will be randomized to one of two conditions:

- Hexyl Acetate and nicotine mixture
 - Ethyl Acetate and nicotine mixture

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

Blocked randomization will be accomplished with a 1:1 ratio of condition assignments with a goal of 60 randomized and completed during the recruitment period. The randomization list will be stored in a password protected REDCap database that will only be accessed by unblinded study personnel.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

The importance of honest reporting will be stressed to participants. Compliance to the instructions for ENDS use will be determined by the daily MyCap surveys. Unused products will be collected, weighed, and recorded. We emphasize that compliance issues should be minimal given that participants are not asked to stop using their typical nicotine products.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

Unblinded study staff will appropriately package the ENDS parts (Battery and cartomizers) into kits for the participants and labeled with a randomization code. The blinded research assistant will not be involved in the packing and labelling of the devices.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

The ENDS batteries and empty cartomizers will be purchased online or in a local storefront in their standard packaging. The ENDS liquid will be purchased from reputable online ENDS liquid and chemical vendors.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

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

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

Trained study staff will be responsible for filling the cartomizers with the appropriate e-liquid ingredients in the laboratory. Participants will be trained on the proper use and storage of the device during the laboratory visit. E-liquids will be dispensed to participants in child-proof bags.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

Participants will have the option to keep the ENDS battery and cartomizer at study completion. Participants will be asked to bring all cartomizers (used and unused) to the research team at the final laboratory visit to be weighed. Unwanted ENDS and empty cartomizers will be disposed of using the appropriate laboratory waste disposal determined by biosafety.

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

Participants can continue using their regular nicotine products during participation. For ethical reasons, we will exclude participants who are currently taking smoking cessation medications (e.g., varenicline, bupropion) in an active attempt to quit using nicotine.

8.0 Number of Subjects and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled, to include all persons who sign consent for the study. If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

120 subjects will be screened to allow for 60 completers – 30 of the MRI completers (both MRI and Laboratory portions) and 30 of the laboratory only completers

8.2 Sample Size Determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

The well-controlled study conditions and straightforward hypotheses allow the study to achieve high statistical power with relatively low sample sizes. The power analysis was conducted under the assumption of fixed effects analysis of variance, power of 80% and pre-specified Type I error probability of 0.05. Previous studies indicate a large amount of variability in the three outcome measures of interest. For subjective reward ratings, for example, which is measured on a 1-7 Likert scale, flavored ratings had a mean of 4.22 and SD of 1.55, whereas unflavored ratings had a mean of 3.11 and SD of 1.55.²¹ For the relative reinforcing value task, the mean for flavored hits was 596.3 with a SD of 520; for unflavored hits the mean was 126.7 with a SD of 90.²¹ Therefore, variability is of the same general order of magnitude as means. It is reasonable to assume that the ratio of effect size to standard deviation (R) is in the range of 1.0 to 1.5, given this prior information. Hence the study is sufficiently powered for the primary analyses, even with some participant dropout, and will be powered for more complex exploratory analyses as well.

8.3 Statistical or Analytic Methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

VTA reactivity will be calculated as the percent change in average BOLD signal in a pre-defined VTA region of interest during inhalation of flavored vs. unflavored aerosol. VTA reactivity will be measured using functional MRI during a blocked puffing paradigm that will include the inhalation of ENDS aerosols that contain the assigned ENDS flavor and an unflavored control aerosol.

Absolute reinforcement will be calculated as the change in the average number of puffs per day during a 10-day use period from the first four-day average to the last four-day average. Ad-lib ENDS use at home will be measured with self-reported daily logs.

Primary analysis: We will conduct one-way repeated measures ANOVAs comparing changes in VTA percent signal change and average puffs from baseline to post-use between the hexyl acetate and ethyl acetate groups. We will calculate partial eta squared (η^2) as a measure of effect size for each ANOVA.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in “HRP-001 SOP- Definitions.”

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that 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. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete each section below if the research involves more than minimal risk to subjects or indicate not applicable.

[Do not type here]

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

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 PI for final inclusion determination prior to randomization. Medical professionals will be consulted as needed. In a similar manner, contraindications for the treatment products will be checked by study staff at each in person visit.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

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

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

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 but can be reported at any time during the study.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

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

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

The study coordinator and the PI will be responsible for the daily oversight of subject safety. The PI 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 PI will seek consultation from a medical professional to make a determination regarding whether the participant is able to continue with the study.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity 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

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Statistical methods will be used to analyze the safety data to determine whether harms are occurring.

9.8 Suspension of research

Describe any conditions that trigger an immediate 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, the trial will be paused for re-evaluation and consultation with medical personnel if a serious adverse event that is determined to be related to the study product occurs.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider all types of risk including physical,

psychological, social, legal, and economic risks. **Note: Loss of confidentiality is a potential risk when conducting human subject research and must be listed here.**

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.
- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

10.1 ENDS use:

- There may be some unknown risks related to the use of ENDS though these risks are not considered to be greater than risks associated with tobacco use from other products.
- The most common side effects associated with using an ENDS 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.
- If stored improperly (in pocket or where the ENDS device can turn on accidentally), overheating of the device may occur, which presents a minor burn risk.
- ENDS liquid contains vegetable glycerin, propylene glycol, nicotine, 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.

Nicotine addiction: Participants will be given a study product that contains nicotine, which is an addictive substance. All participants will be regular nicotine users. Participants will be encouraged to replace their usual nicotine product with the assigned ENDS to avoid increased nicotine exposure during the study period. Participants will be advised to stop or reduce their use of the study e-cigarette if they experience an increase in nicotine addiction symptoms (e.g., increased craving or nicotine withdrawal symptoms). All participants will be provided the Penn State Health “Guide to Quitting Smoking and Vaping” at the end of the trial.

10.2 Nicotine withdrawal symptoms: Abstaining from nicotine prior to the laboratory visits may result in nicotine withdrawal symptoms (e.g. irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, difficulty concentrating).

10.3 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.

10.4 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.

10.5 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).

10.6 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 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.

10.7 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.

10.8 Functional Near Infrared Spectroscopy (fNIRS): There is minimal risk for fNIRS recording. fNIRS is a noninvasive neuroimaging technique. Participants may experience mild transient discomfort on their scalp from the head cap and light optodes. However, this discomfort is not expected to last following removal of the fNIRS equipment.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 14.0.

None

10.2 Potential Benefits to Others

Include benefits to society or others.

This study will determine if certain ENDS flavor chemicals influence brain reward function. The results have the potential to inform our understanding of ENDS addiction, which may assist in tobacco product regulation decisions, addiction prevention efforts, and better treatments for ENDS cessation.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Not applicable

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

All payments will be provided via the Greenphire ClinCard system.

Subjects will be paid according to the following plan at the end of their study participation due to the short length of the study period:

- Remote Screening - \$50
- Pre-Randomization Laboratory Visit - \$75
- Pre- Randomization MRI Scan – \$75 (optional)
- At-Home ENDS Use Surveys - \$50
- Post- Randomization Laboratory Visit - \$75
- Post- Randomization MRI Scan - \$75 and an electronic file of their 3-D anatomical brain image upon request.

Subjects completing all portions of the study could receive up to \$400. Subjects not completing the MRI portion could receive up to \$250.

Subjects will also be given the option to keep the ENDS battery and pods they were provided for at-home use. The study team will dispose of these items if the participants do not want to keep them.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

Not applicable

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:

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.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:

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. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

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.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites, and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Participant visits will take place in the Penn State Center for Nuclear Magnetic Resonance Research.

15.1.1 Penn State Health (PSH) Research Locations

Indicate if any Penn State Health location where this research may take place OR select 'Not Applicable'.

- ☐ Not applicable – research will not take place any at PSH locations
- ☒ Milton S. Hershey Medical Center
- ☐ St. Joseph's Medical Center
- ☐ Berks Cardiology
- ☐ Andrews and Patel
- ☐ Holy Spirit Medical Center
- ☐ Hampden Medical Center
- ☐ Lancaster Medical Center
- ☐ Pennsylvania Psychiatric Institute
- ☐ Community Medical Group
- ☐ Other: [please identify]

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

The study is expected to take 20 months total. In the past, our group has been able to recruit approximately 3 participants per month for clinical trials. We believe that this recruitment timeline is feasible.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Consider outside responsibilities as well as other on-going research for which the PI is responsible. Please only provide a response for the principal investigator – do **not** include information about any other study team members.

Dr. Hobkirk will have 25% funded effort on this project.

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study.

Participants will be referred for medical or psychological services as needed

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties.

Study progress will be discussed on an ongoing basis at weekly lab meetings.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

Not applicable

16.2 Internal PSU Ancillary Reviews

DO NOT ALTER OR DELETE:

Ancillary reviews are reviewed by other compliance groups or individuals within Penn State that inform the IRB's review of a new study or a modification to an existing study.

PSU IRB may set applicable ancillary reviews for your study. Please refer to the HRP-309 Worksheet – Ancillary Review Matrix for more information (found in the CATS Library).

[Do not type here]

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and **the Penn State PI is the lead investigator**, describe the processes to ensure communication among sites in the sections below.

[Do not type here]

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results, and closure of the study.

Not applicable

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Not applicable

18.0 Adverse Event Reporting**18.1 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”. • <i>Reasonable possibility.</i> 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.

18.2 Recording of Adverse Events

Address the frequency and process for eliciting adverse event information from research subject, e.g., “Research subjects will be routinely questioned about adverse events at study visits.”

In the response, incorporate the following as written:

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.

Research subjects will be routinely questioned about adverse events at in person 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 ENDS 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:

- 1) The test finding is accompanied by clinical symptoms
- 2) 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.
- 3) The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- 4) The test finding is considered an adverse event by the investigator.

18.3 Causality and Severity Assessments

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

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.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

For a drug study under an IND, incorporate the following from 21 CFR 312.32 as written – DO NOT ALTER OR DELETE:

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, "IND Safety Report", and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

For a device study under an IDE, incorporate the following from 21 CFR 812.150 as written – DO NOT ALTER OR DELETE:

The Sponsor-Investigator will submit a completed FDA Form 3500A to the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an unanticipated adverse device effect. A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500A will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the Sponsor-Investigator first receives notice of the adverse effect.

If the results of the Sponsor-Investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an unanticipated adverse device effect does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the Sponsor-Investigator will identify all previously submitted reports that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the Sponsor-Investigator will submit additional information concerning the reported adverse effect as requested by the FDA.

Not applicable

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

For a drug study under an IND, incorporate the following from 21 CFR 312.32 into the response, as written:

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor-Investigator will notify the responsible review division of the FDA by telephone or facsimile transmission of any unexpected, fatal, or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Not applicable

18.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

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.

18.6 Unblinding Procedures

Describe the procedures for unblinding study therapy on a subject, including documentation of this in the subject's source document. Include example(s) here why someone might unblind a study. In most cases, the unblinding will be part of managing a serious adverse reaction and will be reported with the serious adverse event. However, in cases where unblinding was not associated with a serious adverse event, such actions should be reported in a timely manner.

If an adverse event requires the subject to be unblinded, the unblinded study personnel will be able to provide that information as needed. Otherwise, participants will not be unblinded to their e-liquid allocation. The principal investigator will begin by reviewing the protocol and establishing guidelines for data and safety monitoring including any additional procedures for unblinding of participants.

18.7 Stopping Rules

In studies with a primary safety endpoint or studies with high risk to study subjects, provide the rules that define the circumstances and procedures for interrupting or stopping the study. If an independent Data and Safety Monitoring (DSMB) or Committee (DSMC) is set up for the study, the same stopping rules should be incorporated into the safety analysis plan as well.

The principal investigator will also develop trial stopping rules to help define the point at which the risks to subjects of continuing the study outweigh the likely benefits. A brief report will be generated and provided to the Penn State IRB.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

Include this section if FDA regulations apply to this study (see “WORKSHEET: Drugs (HRP-306)” and “WORKSHEET: Devices (HRP-307)”. HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (<http://irb.psu.edu>).

Describe how you will ensure that this study is conducted, and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

Indicate who is responsible for monitoring the conduct of the study and specify how often the study will be monitored.

For single-site studies with low risk, it may be appropriate for the principal investigator to monitor the study.

For multi-center studies or single site studies involving significant risk, an independent monitor may be required (e.g., monitoring by the staff of the PSU quality assurance program office(s) or by a clinical research organization).

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 (consent) will be securely transported to the PI’s data entry center. Any additional data that is generated will be stored electronically on the Department 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 (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 or principal investigator 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. Site visits will be conducted by the Penn State research team to ensure that procedures are being executed in compliance with the protocol, and IRB policies.

19.1.2 Safety Monitoring

Include this section if FDA regulations apply to this study (see “WORKSHEET: Drugs (HRP-306)” and “WORKSHEET: Devices (HRP-307)”. HRP-306 and HRP-307 can be accessed by clicking the Library link in CATS IRB (<http://irb.psu.edu>).

Indicate the process for identifying, recording, and reporting adverse events.

Specify roles for adverse event recording and monitoring. Indicate each staff member’s role in the adverse event reporting process. Include the following if applicable:

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.

The **Monitor** will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

The principal investigator will monitor the safety of study participants. 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, and sponsor of all applicable AEs as appropriate. We will consult licensed medical professional at the Penn State College of Medicine and the project faculty mentors as needed. The research coordinator will ensure that AEs are correctly entered into REDCap and complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, and FDA of all Unanticipated Problems/SAE’s.

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for **future undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 below OR the “HRP-598 – Research Data Plan Review Form” regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If there are no plans to use identifiable data/specimens for future, undetermined research, then this section is **NOT applicable**.

[Do not type here]

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored, and the data associated with each specimen.

Research records including survey and interview responses, behavioral task performance, fMRI data, and urine.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

Paper records will be kept in Dr. Hobkirk's research laboratory space. Electronic data will be stored in RedCap or on the HersheyMed Servers. Urine samples will be stored in laboratory freezers in the Psychiatry and Behavioral Health Department.

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate such.

Data will be kept indefinitely for future undetermined research.

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

Study team members will have access to data and specimens at the discretion of the Principal Investigator.

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

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22.0 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.

For research being conducted at Penn State Health or by Penn State Health researchers only: The research data security and integrity plan is submitted using “HRP-598 – Research Data Plan Review Form Application Supplement.”

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 sub-sections of section 22.

For all other research: Complete the following section. Please refer to [PSU Policy AD95](#) for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State’s Policy AD95 or standards or need a consultation regarding data security, please contact Penn State IT – Information Security at security@psu.edu.

See the Research Data Plan Review Form