PennState

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).

Translational Studies on Electronic Cigarette-derived Oxidants and their Long-term Cardiopulmonary Effects

Principal Investigator:
Name: Rebecca Bascom, MD, MPH
Department: Medicine, Division of Pulmonary, Allergy & Critical Care
Telephone: 717-531-2925
E-mail Address: rbascom@pennstatehealth.psu.edu

Version Date:

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

12/15/2023

Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual, When do I have to register my project at ClinicalTrials.gov?" for more information.

NCT05239793

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 INSTRUCTIONS:**
   - 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.
- **Penn State College of Medicine/Penn State Health researchers**: Delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu)**.**
- **Penn State researchers at all other campuses**: Do NOT delete the instructional boxes from the final version of the protocol.

- Add the completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page.

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 Study Submission Guide 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 revisions are made.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Penn State Health:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

2.0 Background

3.0 Inclusion and Exclusion Criteria

4.0 Recruitment Methods

5.0 Consent Process and Documentation

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

7.0 Study Design and Procedures

8.0 Subject Numbers and Statistical Plan

9.0 Data and Safety Monitoring Plan

10.0 Risks

11.0 Potential Benefits to Subjects and Others

12.0 Sharing Results with Subjects

13.0 Subject Payment and/or Travel Reimbursements

14.0 Economic Burden to Subjects

15.0 Resources Available

16.0 Other Approvals

17.0 Multi-Site Study

18.0 Adverse Event Reporting

19.0 Study Monitoring, Auditing and Inspecting

20.0 Future Undetermined Research: Data and Specimen Banking

21.0 References

22.0 Confidentiality, Privacy and Data Management

1.0 Objectives

1.1 Study Objectives

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

To obtain new information regarding the potential cardiopulmonary toxicity resulting from exposure to Electronic Cigarette (EC)-derived oxidants that may lead to long-term disease development.

This is a pilot study on the impact of switching from cigarettes to Electronic Cigarettes (EC) on disease-related clinical symptoms and biomarkers of harm in smokers with preexisting COPD.

We hypothesize that the smokers who switch to EC completely or significantly will experience reduced COPD symptoms, risks of exacerbations, and decreased levels of oxidative stress and inflammation.

These pilot clinical data in smokers with COPD will serve as the basis for future prevention/treatment clinical trials.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have 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).

Degree of compliance with use of EC and improvement of clinical status, determined by the validated CAT: COPD Assessment Test and FEV1.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

Biomarkers of oxidative stress and inflammation.
COPD symptoms.
Risks of exacerbations.
Cardiac Safety endpoints: Major adverse cardiac events (MACE), serious cardiac adverse events (cardiac SAE), cardiac arrhythmia, MI, cardiac failure during the study period or uncontrolled hypertension.

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.

Smokers with COPD have a higher pack-year history and nicotine dependence compared to regular smokers as exemplified by the relatively large proportion of patients diagnosed with COPD that continue to smoke (95%).

This is a translational project which addresses the changing profile of tobacco product use in the United States (US) and the need for data regarding toxicity pathways for new nicotine products. In particular it focuses on critical scientific and clinically relevant gaps relating to oxidants in EC and their potential long-term cardiopulmonary effects.

This project will utilize the NJOY EC which is a product standard for combustible tobacco products that limits the permissible nicotine content to a level that significantly reduces their addictiveness and has the potential to significantly reduce the harms to public health from tobacco use in the United States. (1-3) The NJOY EC is a marketed product that is equivalent to the standardized research electronic cigarette (SREC). The Family Smoking Prevention and Tobacco Control Act gave the FDA jurisdiction to implement such a product standard for cigarettes and other combustible tobacco products. The primary rationale for reducing the permissible nicotine content is to minimize the uptake and addictive use of cigarettes by new cohorts of young people. (4,5)

Over the past 10 years, e-cigs have become increasingly popular in the U.S. where more than 79% of
U.S. adults are currently aware of the devices and 3.7% are using one on a regular basis. (6) Current every-day or someday e-cig use is most prevalent among current smokers (15.9%) and recent ex-smokers (22.0%) and is very uncommon among adult never cigarette smokers (0.4%). (6-8) E-cigs are battery-powered devices that heat and vaporize a liquid mixture (e-liquid), typically containing a vehicle such as propylene glycol (PG) and/or vegetable glycerin (VG) and often, but not always, nicotine and/or flavorings, to produce an aerosol that is inhaled by the user. E-cigs can expose users to several chemicals known to have adverse health effects including nicotine, carbonyls, and volatile organic compounds
(VOCs). The health effects of heated and aerosolized constituents of e-cig liquids, including solvents, flavors, and toxicants, are not completely understood. (9) However, some studies suggest e-cigs, when used exclusively, have a more favorable toxicity profile than tobacco cigarettes. (10, 11)

2.2 Previous Data

Describe any relevant preliminary data.

A significant decline in exposure to acrolein observed among smokers who switched to EC for >6 months.

2.3 Study Rationale

Provide the scientific rationale for the research.

Our pilot study will provide the experience and preliminary data to support the subsequent design of a larger full-scale trial to test this hypothesis in future. (To reiterate, we hypothesize that the smokers who switch to EC completely or significantly will experience reduced COPD symptoms, risks of exacerbations, and decreased levels of oxidative stress and inflammation.) Historically, COPD was considered a disease limited to the lungs and the original Global Obstructive Lung Disease (GOLD) report classified disease severity using only the degree of fixed airflow limitation, as determined by spirometry lung testing. This view was challenged as research demonstrated the complex chronic comorbidities of COPD, particularly chronic heart failure and metabolic syndrome with plasma markers of a pro-thrombotic and pro-inflammatory state. Impaired spirometric lung function is a marker of morbidity and mortality, particularly cardiovascular mortality. The most recent GOLD COPD classification scheme acknowledges an emerging scientific consensus that COPD is no longer a disease only of the lungs, but is associated with systemic inflammation and a wide variety of systemic consequences. The classification scheme includes not only the degree of spirometric airflow limitation (Grades 1-4) but also measures of inflammation (Groups A-D) as classified by a validated patient reported outcome measure (CAT score), exacerbation history and dyspnea scale. We include on our research team a cardiologist, Dr. Naccarelli, to assist with assessing for cardiac events as part of safety monitoring. We are expanding our inclusion criteria to include participants who are GOLD Grade 3 and Groups A-B because these individuals have a similar prognosis to GOLD Grades 1-2 Groups A-B (14). We are also expanding the inclusion criteria to include participants up to age 74 based on their similar prognosis to the younger age groups (15).

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.)

i. Ability to provide informed consent and attend study visits
ii. Ability to read, write and understand English
iii. Adults 21 – 74 years old
iv. Smoke at least 11 cigarettes of a popular brand per day and are willing to switch to the study-provided electronic cigarette for 75% of their daily tobacco use, delivering equivalent levels of nicotine
v. Clinical diagnosis of COPD and evidence of an obstructive airway process including a prolonged expiratory phase ($\geq$ 6 seconds), TLC (total lung capacity) – VA (alveolar volume) $\geq$ 0.5 or FEF 25-75% (forced expiratory flow between 25-75% of vital capacity) <65%
vi. Mild to moderate COPD defined as (GOLD Grade 1-3 and Groups A-B):
    1. COPD with airflow limitation, an FEV1 $\geq$30% predicted, and low exacerbation history <1 exacerbation history in the past year, not requiring hospitalization
        1. AND
    2. Low symptoms (Group A: modified Medical Research Council (mMRC) 0-1, CAT <10
        1. OR
    3. High Symptoms (Group B: mMRC >2, CAT >10)

3.2 Exclusion Criteria

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

i. Active, chronic drug abuse or alcohol abuse problems
ii. Actively changing smoking behavior
iii. Unwilling or unable to provide blood samples
iv. Pregnant, planning to become pregnant, or nursing
v. Use of tobacco products other than cigarettes in the past 30 days
vi. Recent history ($\leq$ 6 months) of myocardial infarction (MI)

vii. Any unstable or life-threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or drug therapy within the past year. Antiarrhythmic drugs include amiodarone, flecainide, IV ibutilide, IV lidocaine, procainamide, propafenone, quinidine, tocainide
viii. Hospitalization for heart failure (NY Heart Association III or IV) within the past year
ix. Uncontrolled hypertension
x. Known allergy to vegetable glycerin and/or propylene glycol
xi. History of seizures or medications to prevent seizures

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.).

3.3.2

- Failure of participant to adhere to protocol requirements.
- Participants may withdraw from study at any time per consent form.

3.3.3 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; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Our sample size includes an estimated drop-out rate of 33%, a number based on previous EC study experience. We will offer subjects the opportunity to continue to be monitored with the scheduled visits and assessments. Withdrawn subjects may be asked to return for an Early Termination Visit.

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 needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

Participants seen by pulmonary colleagues in the Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic will be screened for study eligibility and eligible patients will be made aware of the study. Study Finder will also be utilized in the same manner.

For subject recruitment, we will make use of the existing tobacco research recruitment system (STUDY00002213) and large database of tobacco research volunteers developed as part of our Penn State Tobacco Center of Regulatory Science (TCORS). This database includes over 3,500 individual smokers who have provided basic details on their tobacco use history and demographics as well as contact details. We plan to use this database to select and recruit eligible cigarette smokers to the proposed study. These subjects are primarily from the Hershey/Harrisburg area. The details on where and how participants are recruited for the database are in STUDY0002213. The study team will look through this database for anyone who meets study criteria based on the information gathered in STUDY00002213 (such as smoking status and age). If they meet these basic eligibility requirements, the study team will reach out to them using the Draft Script via the contact information they provided in the database (email, phone, mail), to gauge interest and eligibility. If they are interested, we will confirm eligibility with the phone screening questionnaire.

Potential participants will also be identified through provider referral from the use of a Dear Doctor Letter (sent to other pulmonologists within Penn State Health, and Penn State Health general internal medicine and family and community medicine providers, as well as other pulmonologists/PFT lab medical directors in the south-central PA area), in which case providers will provide potential participants with the study team information, and if potential participants reach out they will be screened with the phone screening questionnaire.

There will also be study flyers posted in the provider workrooms (not patient facing) in the Pulmonary Clinic and in the offices that have received Dear Doctor Letters. In the cases of providers who forward patients to the study team, their eligibility and interest will be determined via the phone screening questionnaire. Additionally, there will be

flyers provided by marketing and communications that will be posted in the Hershey Medical Center and in the Pulmonary Clinic, Pulmonary Function Test Lab and Pulmonary Rehab, as well as in the waiting room of the offices/providers that received the Dear Doctor Letter. The flyers will also be posted in the Pulmonary Function Test Labs at other Penn State locations. Potential participants who reach out the study contact from the flyer will have their eligibility confirmed with the phone screening questionnaire.

The study team will use Facebook/Instagram to recruit with an advertisement that will direct interested participants to our StudyFinder page. Those who contact the study team from StudyFinder will have their eligibility confirmed with the telephone screening questionnaire.

The study team will also be using the on-hold recruitment messaging service. Those who are directed to the study team after expressing interest will have their eligibility confirmed with the telephone screening questionnaire.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant 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.). **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.

Recruitment will be primarily from Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic, Study Finder, the smoking database, flyers posted around Penn State Health, provider referral, Facebook and Instagram, the on-hold messaging service and word of mouth.

4.2.2 Where potential subjects will be recruited.

Potential participants will be recruited in the Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic, Penn State Health Pulmonary Function Test Labs, Penn State Hershey Pulmonary Rehab, or on the telephone (717-531-2925).

4.2.3 When potential subjects will be recruited.

Potential participants will be recruited following completion of preliminary eligibility screening and the participant is deemed to have met preliminary eligibility requirements.

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

Clinic patients seen in the Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic will be screened by study personnel. Those who meet preliminary eligibility criteria will be offered participation in the study at their clinic visit or by telephone. Participants who call in response to seeing Study Finder, the flyers, Facebook/Instagram advertisements, hearing the on-hold message or word of mouth will be screened for eligibility with a telephone questionnaire including pulmonary and cardiac history and review of pulmonary function tests (if available) prior to signing informed consent. Potential participants we call after being identified through the smoking database will be screened for eligibility with a telephone questionnaire prior to scheduling a screening visit. Potential participants who are referred to the study team from other providers will be pre-screened and then contacted to assess interest and further eligibility with the phone screening questionnaire.

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]***

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

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

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

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Consent process will occur in Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic or the PSHMC Clinical Research Center (CRC).

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.

Patients will be informed that participation is entirely voluntarily and will in no way affect their care or access to care at the medical center.

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

OR

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

OR

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

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

Not applicable.

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

Not applicable.

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 be 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.

5.4.7

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 be 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. If not applicable, indicate "not applicable."

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.

Only English-speaking participants will be enrolled.

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.

N/A

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."

N/A

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.

N/A

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

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."

N/A

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.

N/A

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.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

[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]*

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

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

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

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

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

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

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

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

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Identifiers will be destroyed upon completion of the study, including the data analysis. Identifiers will be retained until the completion of the study for all who are screened for the purposes of recruitment analysis.

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

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Prescreening of the Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic and patients sent in from provider referrals will be performed in order to identify patients with current diagnosis of COPD (including review of pulmonary function tests), cardiac history and current smoking status.

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

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Prescreening for eligibility will be needed to ensure the participant currently has a clinical diagnosis of COPD and are GOLD Groups 1-3 and Groups A-B, a current smoking history, and absence of exclusionary medical/cardiac conditions. This will prevent the study team from approaching 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 OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

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.

A panel study design for this pilot, performing repeated measurements in a well-characterized cohort over 3 months. Each participant will serve as his or her own control. The study population will be adults who are active smokers with GOLD Grades 1-3 and Groups A-B COPD. Baselines will be established with duplicate measurements. For their first visit, participants will smoke their usual brand of cigarettes. For the next 3 months, the participants will be asked to reduce smoking by >75% and increase the use of EC using the brand NJOY EC, replacing the equivalent nicotine normally received form cigarettes with the e-cigarette.

Written cigarette reduction information will be provided to all participants. Biological samples (blood and urine) will be collected at baseline and at the end of the study (Month 3). At each clinical visit, nicotine dependence, tobacco use history, acceptability of EC and COPD-related clinical symptoms will be assessed. Spirometric testing and a 6-minute walk will be performed at baseline and at the end of the study (Month 3). Exhaled carbon monoxide will be measured at every in-person study visit as a subject characterization to assess their current cigarette usage as e-cigarettes will not cause carbon monoxide production. An electrocardiogram (ECG) will be performed at baseline and at the end of the study (Month 3). Interim ECGs will be obtained if deemed necessary by Dr. Bascom and Dr. Naccarelli. A follow-up visit will occur at 3 months from start of the trial to capture current tobacco use. Safety monitoring will include assessment for cardiac endpoints. An Early Termination Visit may occur at any point at discretion of the Principal Investigator if a participant will not be completing the study.

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.)
-WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Please see Table 1 below for schedule of events.

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.

7.2.1 Visit 1/Day 1 (Screening/Baseline): Clinical Research Center (CRC)

1. Consent process; sign consent form
2. Assess inclusion/exclusion criteria
3. Clinical Assessment:
    a. COPD Exacerbation History Questionnaire
    b. COPD assessment
        i. GOLD staging:
            1. Spirometry
            2. 6-minute walk
            3. CAT score and mMRC question
    c. Cardiac Assessment:
        i. Endpoints assessed via medical record and participant report
        ii. Electrocardiogram (may be performed at other visits if deemed necessary by principal investigator)
        iii. Vital signs
    d. Height and weight
4. Exhaled carbon monoxide measurement
5. Collection of biosamples:
    a. Blood – approximately 20ml
    b. Urine
6. Analyses on biosamples:
    a. Inflammation markers in blood: CRP, TNFa, IL-1B, IL-6, IL-8
    b. Oxidative stress markers
    c. Aldehyde exposure
    d. Cigarette smoke exposure cotinine
    e. Urine dipstick pregnancy test
    f. CBC
7. CMP Questionnaires:
    a. Baseline Nicotine Usage completed by participant
    b. PROMIS questionnaires:
        i. Nicotine Dependence for Daily and Nondaily Smokers – Short Form 8a
        ii. Negative Health Expectancies for Daily and Nondaily Smokers – Short Form 6a

iii. Emotional and Sensory Expectancies for Daily and Nondaily Smokers – Short Form – 6a
iv. Negative Psychological Expectancies for Daily and Nondaily Smokers – Short Form 6a
v. Coping Expectancies for Daily and Nondaily Smokers – Short Form 4a
vi. Companion Items used by the PROMIS Smoking Initiative

c. St. George's Respiratory Questionnaire (SGRQ)

8. Provide participant with EC and NJOY pods
9. Collect concomitant medications
10. Provide a diary to record cigarette and e-cigarette use
11. Provide a "Reminder Message"
12. Provide a copy of "Consumer Surgeon General Report Booklet"
13. Provide a copy of "Cessation Surgeon General Consumer Guide"

All future visit dates are based on the date of Visit 1/Day 1.

7.2.2 Phone Call Visits/Weeks 1 and 2 (Visits 2 and 3); Months 1 and 2, (Visits 4 and 5)

1. Phone Assessment which includes product usage, tobacco usage, motivation suggestions and a visit reminder
2. Adverse Events
3. Concomitant Medications
4. PROMIS Questionnaire: Nicotine Dependence for Daily and Nondaily Smokers – Short Form 4a

7.2.3 Visit 6/Month 3– Clinical Research Center (CRC)

1. Clinical Assessment:
   a. COPD Exacerbation History Questionnaire
   b. COPD assessment
      i. GOLD staging:
         1. Spirometry
         2. 6-minute walk
         3. CAT score and mMRC question
   c. Cardiac Assessment:
      i. Endpoints assessed via medical record and participant report
      ii. Electrocardiogram (may be performed at other visits if deemed necessary by principal investigator)
      iii. Vital signs
   d. Weight
2. Collection of biosamples:
   a. Blood – approximately 20ml
   b. Urine
3. Analyses on biosamples:
   a. Inflammation markers in blood: CRP, TNFa, IL-1B, IL-6, IL-8
   b. Oxidative stress markers

c. Aldehyde exposure
d. Cigarette smoke exposure cotinine
e. Urine dipstick pregnancy test
f. CBC

CMP4. Questionnaires:

a. In Person Nicotine Usage completed by participant
b. PROMIS questionnaires:
i. Nicotine Dependence for Daily and Nondaily Smokers – Short Form 8a
ii. Negative Health Expectancies for Daily and Nondaily Smokers – Short Form 6a
iii. Emotional and Sensory Expectancies for Daily and Nondaily Smokers – Short Form 6a
iv. Negative Psychological Expectancies for Daily and Nondaily Smokers – Short Form 6a
v. Coping expectancies for Daily and Nondaily Smokers – Short Form 4a
c. St George's Respiratory Questionnaire

5. Collect all used and unused NJOY pods
6. Collect concomitant medications
7. Collect the diary used to record cigarette and e-cigarette use
8. Provide a copy of "Consumer Surgeon General Report Booklet"
9. Provide a copy of "Cessation Surgeon General Consumer Guide"
10. Exhaled carbon monoxide measurement

7.2.7 Early Termination Visit: Clinical Research Center (CRC)

1. Clinical Assessment:
a. COPD Exacerbation History Questionnaire
b. *COPD assessment
i. GOLD staging:
1. Spirometry
2. 6-minute walk
3. CAT score and mMRC question
c. *Cardiac Assessment:
i. Endpoints assessed via medical record and participant report
ii. Electrocardiogram (may be performed at other visits if deemed necessary by principal investigator)
iii. Vital signs
d. Weight
2. *Collection of biosamples:
a. Blood – approximately 20ml
b. Urine
3. Analyses on biosamples:
a.* Inflammation markers in blood: CRP, TNFa, IL-1B, IL-6, IL-8
b. *Oxidative stress markers
c. *Aldehyde exposure
d. *Cigarette smoke exposure cotinine
e. Urine dipstick pregnancy test

f. *CBC and CMP

4. Questionnaires:
    a. In Person Nicotine Usage completed by participant
    b. *PROMIS questionnaires:
        i. Nicotine Dependence for Daily and Nondaily Smokers – Short Form 8a
        ii. Negative Health Expectancies for Daily and Nondaily Smokers – Short Form 6a
        iii. Emotional and Sensory Expectancies for Daily and Nondaily Smokers – Short Form 6a
        iv. Negative Psychological Expectancies for Daily and Nondaily Smokers – Short Form 6a
        v. Coping expectancies for Daily and Nondaily Smokers – Short Form 4a
    c. *St George's Respiratory Questionnaire
5. Collect all used and unused NJOY pods
6. Collect concomitant medications
7. Collect the diary used to record cigarette and e-cigarette use
8. Provide a copy of “Consumer Surgeon General Report Booklet”
9. Provide a copy of “Cessation Surgeon General Consumer Guide”
10. *Exhaled carbon monoxide measurement

***these procedures will be done as needed by discretion of the Principal Investigator**

Table 1. Schedule of Events

Time Period	Screening/Baseline	1 week	2 week	1 month	2 month	3 month
Type of Visit	In-person	Phone call[c]	Phone call[c]	Phone call[c]	Phone call[c]	In-person
Visit	1	2	3	4	5	6
Day	1	7	14	30	60	90
Visit Window	-	± 1 day	± 1 day	± 3 days	± 3 days	± 3 days
Study Procedure	-	-	-	-	-	-
Consent	X	-	-	-	-	-
Inclusion/Exclusion Criteria	X	-	-	-	-	-
Past Medical History	X	-	-	-	-	-
PROMIS Questionnaires	X	X[d]	X[d]	X[d]	X[d]	X
Nicotine Usage Questionnaire	X	-	-	-	-	X
SGRQ	X	-	-	-	-	X
CAT/mMRC	X	-	-	-	-	X
PFTs (spirometry/6MWT)	X	-	-	-	-	X
Height/Weight[a]	X	-	-	-	-	X
ECG	X	-	-	-	-	X
Vital Signs[b]	X	-	-	-	-	X
COPD Exacerbation Questionnaire	X	-	-	-	-	X
Blood sample collection	X	-	-	-	-	X
Urine sample collection	X	-	-	-	-	X
Provide new patient diaries	X	-	-	-	-	-
Collect completed patient diaries	-	-	-	-	-	X
Provide smoking cessation materials	X	-	-	-	-	X
Dispense study product	X	-	-	-	-	-
Collect study product	-	-	-	-	-	X
Phone Assessment[c]	-	X	X	X	X	-
Adverse Events	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X

[a]Height to be collect at Visit 1 only
[b]Vital signs are to include heart rate, systolic blood pressure, diastolic blood pressure, SpO_2
[c]Phone assessment will include product usage, tobacco usage, motivation suggestions, and visit reminder
[d]Only PROMIS Questionnaire: Nicotine Dependence for Daily and Nondaily Smokers – Short Form 4a is to be administered during phone visit

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.

Participants will be involved in the study for a total of 3 months. Screening/Baseline and Month 3 visits will last approximately 3 hours. Phone calls will last approximately 15 minutes.

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).

We will use NJOY EC, Classic Tobacco 5%, purchased from NJOY, Inc. The NJOY EC is a closed-system device that contains 2 main components: a disposable pod that contains liquid and a heating coil, and a USB rechargeable battery. The disposable pods contain 1.9 ml of EC liquid and contain 5% nicotine strength by weight. The device is rechargeable with a USB charging dock. The NJOY EC device meets battery and electrical testing standards.

The initial proposal was to use the NIDA Standardized Electronic Cigarette (SREC) because it has known nicotine pharmacokinetics and it is known to deliver low concentrations of toxicants relative to both cigarettes and some other EC. (12, 13) However, the EC company manufacturing the NIDA SREC product has experienced technical difficulties as it moved from producing small numbers of this EC to manufacturing a large number of EC for numerous clinical trials. Until these problems have been resolved, we are unable to use this product. We chose to use NJOY as it is currently commercially available to consumers and it is a NIDA product equivalent to SREC.

7.4.2 Treatment Regimen

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

Following the baseline visit, all participants will be provided an NJOY device, charger, and pods and will be asked to reduce cigarette smoking by >75% and instructed to increase the use of EC as they reduce their cigarette smoking. Participants will be provided with the number of pods equivalent to their usual cigarette pack/day.

7.4.3 Method for Assigning Subject to Treatment Groups

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

N/A

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

Participants will be asked to complete a diary of use and will be asked questions about number of cigarettes and NJOY pods used and biomarkers of exposure will be obtained throughout the course of the study.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

N/A

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.

NJOY devices will be purchased from NJOY, Inc. in its standard packaging and shipped to Penn State and will be received by study staff. Pre-filled, sealed, disposable pods containing 1.9 ml of EC liquid will also be purchased from NJOY, Inc. The research team will maintain the certificates of analysis or lot information for the NJOY products used in the study.

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.

EC devices and liquids will be stored at room temperature in a locked space in the College of Medicine (Room C6627) that is only accessible by the study coordinator and

approved research staff involved in this study. A service provided by Penn State will monitor and record the temperature/humidity of the room.

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.

The pods will come pre-filled in sealed packages. They will be prepared for participants by staff and stored with unique identifiers. Staff will appropriately package kits containing the NJOY device and a supply of pods for the participants. NJOY will be dispensed by research staff at the CRC during the participant's first visit and at subsequent in-person visits.

Participants will be provided a three month's supply of pods at a time. During in-person visits, pods will be provided to participants. If participant's supply of pods will not last for the three months, the participant will be asked to contact the study team.

If at any time the NJOY device becomes defective and not working, participants will be asked to notify the study team at which time a replacement device will be offered and the participant will be asked to return the defective item.

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 be instructed to return all used and unused e-liquid pods to the study at each in-person visit to monitor use. Accountability logs will be completed by study staff to determine product usage. During the last in-person visit in the CRC, the research staff will dispose of the EC. Any unused pods that are returned at the last in-person visit will be destroyed on site according to the general policy for drug disposal by the Investigational Drug Pharmacy.

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.

A list of the participant's medications will be collected and updated at each visit. Antiarrhythmic medications and medications to treat seizures are not permitted during the study.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. 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 if applicable (i.e., numbers of subjects excluding screen failures.)

We will enroll 30 patients (equal men and women), anticipating a 33% dropout rate which is based on previous EC studies performed at PSU.

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.

This is a pilot design study with repeated data collection in a panel of individuals; each individual serving as their own control (n = 30, anticipate final sample n= 20). We will obtain preliminary data required for designing larger-scale hypothesis testing trial in COPD patients. To our knowledge, the pulmonary impact of switching to EC in smokers with COPD has not been studied in any clinical trial.

8.3 Statistical methods

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

The primary endpoints are cigarettes per day (CPD) and reduction in exacerbations. Secondary endpoints include CAT scores, FEV1, 6-minute walk distance, patient reported outcomes, and biomarkers of exposure and harm. Due to the exploratory nature of this aim, most of the statistical analysis for this study will be descriptive and summary statistics will be generated for study endpoints. Sample size was selected based upon getting adequate data for this purpose with the addition of ten participants for anticipated dropouts and non-compliers.

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 the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as 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 PI and research staff will be responsible for the daily oversight of subject safety. Subjects will be seen by research staff while in the study that will assess adverse events and take appropriate medical actions if necessary. The Safety Monitor will review AEs on a weekly basis and study staff will discuss subject's experiences during meetings when necessary. In addition, the study statistician will prepare a cumulative report of all data points listed below for the Data and Safety Monitoring Board to review every 6 months after recruitment begins.

9.2 Data that are reviewed

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

The Data and Safety Monitor Report will include:

a. Accrual and retention.
b. Baseline sociodemographic characteristics.
c. Adverse events and serious adverse events.
d. Protocol deviations/violations.
e. Participant's ability to achieve study requirements.
f. Changes in cigarette consumption from baseline.
g. Exhaled carbon monoxide change from baseline.
h. Changes in lung function via pulmonary lung function tests.
i. Changes in lung function via the Clinical COPD assessment.
j. 6-minute walk distance.
k. Questionnaires.
l. Laboratory results

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).

Safety data and adverse event information will be collected at study visits and entered directly into REDCap. At every study visit, participants will be asked a series of standard questions that would trigger an assessment for an adverse event to be documented. Adverse event information can also be given voluntarily by participants between study visits. An adverse event log will be used to document the description of the adverse event including, start/stop dates of event, type, grade, attribution to the study treatment, expected/unexpected, and action taken.

9.4 Frequency of data collection

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

Adverse event information and safety data will be collected at each study visit but can be reported at any time during the study.

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.

A Data Safety Monitoring Board has been established to review the data that will include Richard Bernstein, MD, Department of Medicine and Division of Pulmonary Allergy and Critical Care Medicine, Director, Pulmonary Function Laboratory (pulmonary physician and board chair); Jessica Yingst, DrPH, Department of Public Health Sciences, Assistant Professor, Division of Health Services and Behavioral Research; Gerald Naccarelli, MD, Professor of Medicine/Chief, Division of Cardiology (ethics) and Sophia Allen, PhD, Department of Public Health Sciences, Assistant Professor. The committee will review the report prepared every six months by Junjia “Jay” Zhu, MS, PhD, Assistant Professor in Biostatistics and Bioinformatics (study statistician) and make appropriate recommendations to continue research as is, continue research with modification, or discontinue research in the event of significant efficacy issues or unacceptable adverse events. A copy of the committee’s review of the Data and Safety Monitoring Report will be shared with Penn State IRB and any other appropriate regulatory bodies.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

A Data and Safety Monitoring Report with cumulative data will be generated every six months after recruitment begins.

9.7 Statistical tests

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

Basic descriptive statistical methods will be used to analyze the safety data to determine whether harms are occurring. Changes from the baseline in cigarette consumption, exhaled carbon monoxide, pulmonary function and general health measures will be calculated. In addition, the accrual and retention-dropout rate, completion rate, and the proportions of adverse events and serious adverse events will be generated.

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Due to the low risk of the study treatment, it is unlikely that there will be a need to suspend the research. However, should the committee identify any issues after reviewing the cumulative data, these recommendations will be followed.

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.

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.

Study Participation Risks:

Loss of Confidentiality: There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the study team, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Test Procedure Risks:

Standard Venipuncture: The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a bruise at the site of puncture. Less common risks include a small blood clot,

infection or bleeding at the puncture site, and on rare occasions fainting during the procedure. Approximately 20ml of blood will be taken at the specified visits.

Pulmonary Function Tests: Pulmonary Function Tests will be performed at various time points. Risks associated with testing may include lightheadedness, fainting, shortness of breath, or chest tightness.

6-minute Walk: 6-minute walk distance will be performed at various time points. Risks associated with testing may include shortness of breath, chest tightness, tiredness, lightheadedness, dizziness or fainting, incoordination, or confusion while walking.

Electrocardiograms (ECG): Electrocardiograms will be done at various time points. An ECG measures the electrical activity of the heart. Participants may experience mild irritation, slight redness, or itching at the sites on the skin where the recording patches are placed.

NJOY use: There may be some unknown risk related to the use of ECs. The most common side effects associated with using an EC are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, sore throat, mouth ulcers, dizziness, headache, nausea, and hiccups. Participants who have asthma have a risk of asthma attacks when using the NJOY.

a. EC liquid contains vegetable glycerin, propylene glycol, and flavorings. It is possible that participants may have an allergy to one or more of these ingredients. Participants with known allergies to these substances will be excluded from the study. The most common reported allergic reaction to these substances is contact dermatitis (or rash).
b. There are reports that some people who use ECs have experienced seizures, with most involving youth or young adult users. Participants with a history of seizures or take medications to prevent seizures will be excluded from the study.
c. There have been some reports of serious lung illnesses among those who used ECs and even some cases of death as a result. The cause of all deaths has not been identified. The investigations being conducted by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have found that the majority of people experiencing these illnesses were using EC products that contained tetrahydrocannabinol (THC) and/or products that were bought off the street and not from retail establishments. The EC products used in this study do not contain THC and were bought from manufacturers where quality testing and control is performed. Nonetheless, participants will be advised to call their doctor immediately if they experience cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, or fever after using their EC. Participants will be told to only use the EC and liquid pods (cartridges) given to them by the researchers and to not tamper with their EC or use other liquids with the EC device.

New Pregnancy or intention to become pregnant: Nicotine from ECs is known to be harmful to the developing human fetus. Women who are pregnant or are nursing a child may not participate in this research study. Participants must agree to take reasonable and necessary precautions against becoming pregnant during the study period.

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.

Specimens will be labeled with the last 4 digits of the protocol number followed by subject number, visit number and date of collection on the storage vials. It will not contain any identifying information. The linkage list connecting the sample to the participant will be maintained in a separate protected location. In the event of publication, no identifying information will be included.

The linkage list will be maintained indefinitely.

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.

Participants will receive information regarding smoking reduction strategies and information on cessation at the beginning and end of the study (Consumer Surgeon General Report Booklet and Cessation Surgeon General Consumer Guide). There are no other expected benefits to the participant by participating in the study.

11.2 Potential Benefits to Others

Include benefits to society or others.

The knowledge gained from these studies will be used to help better understand the mechanisms involved in tobacco smoking and health and the benefits of switching to potentially lower risk products.

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.

Study results will not be shared with participants.

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.

Participants will be compensated $40 for completing each of the Screening/Baseline and Month 3 in-person visit. Participants will also be paid an additional $30 at the Month 3 visit for completing the study. If you withdraw from the study and complete the Early Termination Visit, you will be paid $40.00 at that visit. The maximum amount a participant can be paid is a total of $110.

14.0 Economic Burden to Subjects

14.1 Costs

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

The only cost to participant would be in regards to traveling expenses to the CRC appointments.

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 the participants 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.

In-person visits will occur at the CRC located at Penn State Hershey Medical Center. Research specimens, which include blood and urine samples will be tested in Dr. Sinha's lab. CBC and CMP will be processed by the clinical laboratory.

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 Penn State Hershey Medical Center Pulmonary Division's Outpatient Clinic sees numerous patients diagnosed with COPD and the recruitment target is well within the capacity of the busy pulmonary clinic. We have previously recruited for clinical trials from this population.

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. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Drs. Bascom and Sinha have met regularly for the development of this application, and continue to meet to assure smooth implementation. Dr. Bascom, RO1 co-investigator,

will have principal responsibility for oversight and implementation of Aim 3 (this clinical study). A portion of her time is allocated to clinical trials, and this is within the scope of that activity.

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, if applicable.

All of our participants will be seen by appropriately trained research staff. It is not anticipated that participants will need any medical or psychological resources as a result of being in this study. Safety of the participants will be monitored by the research staff throughout the study. Any immediate urgent health problem will result in accompanying the participant to the ER, which is located in the same building as the clinical research center.

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, if applicable.

Weekly study coordinator meetings will be the site of orientation and training.

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.).

N/A

16.2 Internal PSU Committee Approvals

Check all that apply:

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

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

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

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

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

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

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

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

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee.

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.

N/A

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.

N/A

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.

N/A

17.4 Subject Enrollment

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

N/A

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.

N/A

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.

N/A

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". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

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

18.2 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 participants will be routinely questioned about adverse events during in-person and telephone 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 device 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 participant'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 3500Ato 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 3500Awill 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 3500Aas 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 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.

N/A

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.

N/A

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 participant 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.

N/A

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.

No formal a priori statistical stopping rules will be used for interim monitoring of the primary or secondary endpoints. Analyses will be performed and comprise of endpoints associated with safety and study integrity (i.e. recruitment rate, completion rate, rates of SAEs/AEs, and any other variables that are requested from the Data and Safety Monitoring Committee. A bi-annual summary report of these analyses will be prepared by the study statistician for the committee to review. The committee will use these reports as the primary basis assessing data quality and subject safety, and if necessary making recommendations of amendment to the protocol or stopping the trial.

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).

Dr. Bascom will be responsible for the overall design, conduct and monitoring of the study. Data generation and documentation will follow Good Clinical Practice guidelines.

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 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.

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 Safety Monitor (Richard Bernstein, MD) is a licensed medical professional who will make the final assessments and causality of AEs. He will be available to answer any questions concerning AEs. Dr. Gerald Naccarelli, MD is the co-Safety Monitor and is also a licensed medical professional who is available to assist in final assessments and causality of AEs. He will also be available to answer any questions concerning AEs.

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 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

[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.

Remnant specimens (blood and urine) collected during the study will be banked for future undetermined research. Specimens will be stored with last four digits of the protocol number followed by subject number, visit number and date of collection. At the conclusion of the data collection and verification, the linkage list will be maintained. All other identifiable data associated with the ID code will be retained in REDCap. Questionnaire data collected during the study that is used for future undetermined research will be de-identified.

20.2 Location of storage

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

Specimens will be stored in freezers in the locked lab spaces of Dr. Sinha in the Cancer Institute.
Questionnaire data will be stored within REDCap.

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 as such.

Questionnaire data and specimens will be stored indefinitely.

20.4 Access to data and/or specimens

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

The lab managers, technicians, study coordinators, and PI will have access to the freezer rooms where the specimens will be stored. The researchers will have access to the stored data in REDCap, although role-specific rights will be granted as minimally necessary.

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.

Investigators who are interested in obtaining specimens and/or data from this project for ancillary studies will first be required to submit a detailed written proposal to Dr. Sinha. If the proposal is approved, only de-identified data will be released to the investigator.

20.6 Process for returning results

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

Investigators will be required to provide the results to the study team and PI.

21.0 References

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

1. Benowitz NL, Donny EC, Hatsukami DK. Reduced nicotine content cigarettes, e-cigarettes and the cigarette end game. Addiction. 2017;112(1):6-7.

2. Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, et al. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. N Engl J Med. 2014;373(14):1340-9.

3. Donny EC, Hatsukami DK, Benowitz NL, Sved AF, Tidey JW, Cassidy RN. Reduced nicotine product standards for combustible tobacco: building an empirical basis for effective regulation. Prev Med. 2014;68: 17-22.

4. Benowitz HL, Henningfield JE, Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med. 1994;331(2):123-5.

5. Benowitz NL, Henningfiled JE. Reducing the nicotine content to make cigarettes less addictive. Tob Control. 2013;22 Suppl 1:i14-7.

6. Schoenborn CA, Gindi RM. Electronic Cigarette Use Among Adults: United States, 2014. NCHS Data Brief. 2015(217):1-8.

7. Wilson FA, Wang Y. Recent Findings on the Prevalence of E-Cigarette Use Among Adults in the U.S. Am J Prev Med. 2017;52(3):385-90

8. Hammett E, Veldheer S, Yingst J, Hrabovsky S, Foulds J. Characteristics, use patterns and perceptions of electronic cigarette users who were never traditional cigarette smokers. Addict Behav. 2017;65:92-7

9. U. S. Department of Health and Human Services, E-cigarette Use among Youth and Young Adults: A Report of the Surgeon General. Atlanta, US: U. S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.

10. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BW, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versu cigarette smokers. Nicotine Tob Res. 2014;17(6):704-9

11. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Ann Intern Med. 2017;166(6):390-400.

12. Bitzer ZT, Goel R, Reilly SM, Bhangu G, Trushin N, Foulds J, et al. Emissions of Free Radicals, Carbonyls, and Nicotine from the NIDA Standardized Research Electronic Cigarette and Comparison to Similar Commercial Devices. Chem Res Toxicol. 2019;32(1):130-8.

13. National Institute on Drug Abuse. [2018].Supplemental Information for NIDA e-cig. Available from: https://www.drugabuse.gov/research/research-data-measures-resources/nida-drug-supply-program/supplemental-information-nida-e-cig.

14. Le, L. A. K., Johannessen, A., Hardie, J. A., Johansen, O. E., Gulsvik, A., Vikse, B. E., & Bakke, P. (2019). *Prevalence and prognostic ability of the gold 2017 classification compared to the gold 2011 classification in a Norwegian COPD cohort*. International journal of chronic obstructive pulmonary disease. Retrieved November 21, 2022, from https://pubmed.ncbi.nlm.nih.gov/31413559/

15. Fernández-García, A.; Pérez-Ríos, M.; Fernández-Villar, A.; Naveira, G.; Candal-Pedreira, C.; Santiago-Pérez, M.I.; Represas-Represas, C.; Malvar-Pintos, A.; Cerdeira-Caramés, S.; Ruano-Raviña, A. Four Decades of COPD Mortality Trends: Analysis of Trends and Multiple Causes of Death. J. Clin. Med. 2021, 10, 1117. https:// doi.org/10.3390/jcm10051117

22.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form