PennState

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

Protocol Title:

Does Switching to Nicotine Containing Electronic Cigarettes Reduce Health Risk Markers?

Principal Investigator:

Jonathan Foulds, PhD
Public Health Sciences
(717) 531-3504
jfoulds@psu.edu

Version Date:

6-28-23

Clinicaltrials.gov Registration #: NCT03625986

Table of Contents

1.0 Objectives

1.1 Study Objectives

Our long term goal is to understand the likely health effects of cigarette smokers switching to a Standardized Research E-Cig (SREC) and to assess the role of nicotine delivery on switching, acceptability and markers of health outcomes. The specific objective of this proposal is to recruit a cohort of 240 current exclusive daily cigarette smokers and to measure a comprehensive battery of health markers at baseline and at 3 and 6 weeks after attempting to switch completely to SRECs containing either zero or 58 mg/ml nicotine in a randomized double-blind, placebo-controlled design with the following three specific aims:

1.1.1 **Aim 1:** To characterize the short-term effects of attempting to switch from traditional cigarette smoking to a Standardized Research E-Cig from baseline to 6 weeks using a comprehensive battery of measures (e.g. carcinogen biomarker (NNAL), pulmonary function testing, Holter EKG, exhaled CO, and cotinine, BP etc.).

1.1.1.1 Our hypothesis is that attempting to switch to a SREC will result in a reduction in markers of harms to health, as compared with the baseline (exclusive cigarette smoking) measures.

1.1.2 **Aim 2:** To compare the effects of switching to a standardized research electronic cigarette (SREC) with pods containing 58 mg/ml nicotine liquid versus 0 mg/ml nicotine liquid on smoking behavior and changes in health markers at 6 weeks post-switching.

1.1.2.1 Our hypothesis is that nicotine-containing SRECs will facilitate switching from smoking more efficiently than zero nicotine SRECs and will result in a significantly greater improvement in markers of health risk, but will conversely result in higher ratings of dependence on the SREC (as compared to the zero nicotine SREC) at 6 weeks post-switching (after controlling for baseline measures).

1.1.2.2 We also hypothesize that the nicotine-containing SRECs, (as compared with the zero nicotine SRECs, after controlling for baseline) will result in a lower total score for the withdrawal items on the MNWS and lower mean scores on ratings of cigarette craving, during the first week of the trial.

1.1.3 **Aim 3**: At the end of each participant's 6 week participation, they will be provided with information about the health effects of tobacco product use, how to purchase their own electronic cigarette and supplies if they wish to continue using one, and sources of assistance to quit smoking. They will then be asked to complete telephone and online survey four weeks later (10 weeks after switching).

1.1.3.1 Our hypothesis is that participants randomized to nicotine-containing SRECs (as compared with those randomized to zero nicotine liquid) will be more likely to continue to try to abstain from cigarettes and to continue to use an e-cig at week 10 follow-up.

1.2 Primary Study Endpoints

The primary endpoint for the study is creatinine-corrected urinary NNAL concentration at 6 weeks (after switching).

1.3 Secondary Study Endpoints

Secondary outcomes for the study include changes in pulmonary function (FEV-1), tobacco-related toxicant concentrations, such as exhaled CO, EKG markers (HRV, PVCS, ST elevations, WRS duration),

urine cotinine, and blood pressure at 6 weeks, controlling for baseline measures. In addition, nicotine withdrawal and cravings, measured on the MNWS, at 1 week controlling for baseline. Finally, the average number of cigarettes smoked per day (CPD) and measures of dependence (e.g. FTND, PSECDI) will be analyzed. Outcomes at the 10 week telephone follow-up include the average number of cigarettes smoked per day in the week prior to the follow-up call, the number of days on which an e-cig was used in the previous 21 days, and the self-reported cigarette abstinence (zero cigarettes smoked in the prior week).

2.0 Background

2.1 Scientific Background and Gaps

Tobacco smoking is the leading preventable cause of premature morbidity and mortality in the U.S.[1] and cessation provides immediate and sustained improvement in health.[2] Cigarette smoking harms almost every organ in the body, but the lungs and the cardiovascular system are particularly affected. Thus, cigarette smokers aged 35-64 have a greater than 3-fold risk of death from ischemic heart disease and cerebrovascular diseases and more than a 10-fold risk of death from chronic airway obstruction or lung cancer, compared with never cigarette smokers.[1] These effects and the mechanisms causing them are relatively well understood. Similarly, there is clear evidence that the risks of suffering from and eventually being killed by these smoking- caused diseases reduce significantly if a smoker quits smoking completely. Thus, the clear message for smokers is that the single best thing they can do for their health is to quit smoking completely.

Over the past ten years, a new inhaled nicotine device, commonly referred to as an electronic cigarette (e-cig), has become increasingly popular around the world, particularly in the United States where more than 79% of US adults are currently aware of the devices and 3.7% are using one on a regular basis.[3] Current 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%).[3-5] As the popularity of these devices has increased, the types of devices and the associated products available to users have diversified, making it difficult for users and non-users alike to understand the devices and their potential harms or benefits.

Though e-cigs are generally considered to be safer than traditional combustible cigarettes, the devices do deliver fine particles when the solvents (propylene glycol, vegetable glycerin, flavors, additives, and nicotine) are aerosolized and adequate assessments of cardiovascular and pulmonary health outcomes related to e-cig use are lacking.[6] Recently, the National Institute on Drug Abuse (NIDA) developed a Standardized Research E-Cig (SREC) which is available in both medium (58 mg/ml) and placebo (zero mg/ml) nicotine liquid concentrations. The availability of this new device offers researchers the possibility of testing the likely health effects on users who are attempting to switch from cigarette smoking to e-cigs.

2.2 Previous Data

One study found that after 5 minutes of ad lib e-cigarette use, healthy adult cigarette smokers showed an increase in airway resistance, but no effect on other spirometry parameters such as forced vital capacity (FVC), forced expiratory volume in 1 second FEV1), and ratios of these values (FEV1/FVC).[7] Other studies have examined changes in lung and cardiovascular function over a longer time in smokers attempting to quit smoking by switching to e-cigs. For example, Cibella et al[8] found that smokers who completely switched to e-cigs and quit smoking showed steady improvement in their FEV (25-75%) and improvement in respiratory symptoms, including the time period when many continued using their e-cigs. This is consistent with the idea that smoking has a more severe adverse effect on lung function than e-cig use. Laboratory studies have also examined some acute cardiovascular effects of e-cig use and compared these with acute cigarette smoking. Farsalinos et al[9] examined the immediate effects of electronic cigarette use on left ventricular (LV) function, compared to the well-documented acute

adverse effects of smoking. They found that although acute smoking caused a delay in myocardial relaxation, electronic cigarette use had no such immediate effects. Farsalinos et al[10] also examined the effects on heart rate and blood pressure of switching from cigarettes to e-cigs in a smoking cessation trial, and reported that smokers who reduce or quit smoking by switching to e-cigarettes may lower their systolic BP in the long term. While these and other studies confirm the known cardiopulmonary effects of acute smoke and other nicotine aerosol inhalation, they provide only limited information about the cardiopulmonary effects of e-cig use because they typically study the effects of only one type of e-cig (usually a first generation or "cigalike" model), and focus more on the effects of change in smoking behavior rather than carefully assessing the effects of e-cig use per se. These studies have also included relatively basic cardiovascular outcomes (e.g., blood pressure and heart rate). These acute laboratory studies also typically selected a single device to study and were unable to examine the effects of chronic use of these products. One study has examined some effects in existing cohorts of (a) e-cig users who had quit smoking an average of 8 months earlier (b) cigarette smokers and (c) dual users over 24 months.[11] This study found that exclusive e-cig users were most likely to remain tobacco abstinent (61%), but that dual users were more likely to return to exclusive smoking than to quit smoking. There were few serious adverse events and detailed cardiopulmonary measures were not systematically recorded. The only significant finding on health outcomes was that dual users experienced improvements in self-rated health compared with those who continued smoking. An earlier one year follow-up on these cohorts found that the exclusive e-cig users reported a small but significant improvement in self-reported health as compared with the smokers.[12]

2.3 Study Rationale

Study of the health effects of e-cigs is in its infancy, and there are very few randomized placebo-controlled studies on the effects of switching to a well-characterized standardized e-cigarette on subclinical markers of cardiopulmonary and health risks. We propose to conduct what would be the first such study in the United States.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Aged 21-70, verified by photo identification
2. Smoke ≥5 cigarettes per day for at least the past 12 months
3. Smoke regular, filtered cigarettes or machine-rolled cigarettes with a filter
4. Exhaled CO measurement ≥6 ppm at baseline visit
5. No serious quit attempt in past 7 days. This includes use of any FDA approved smoking cessation medication (varenicline, bupropion [used specifically as a quitting aid], patch, gum, lozenge, inhaler, and nasal spray) in the past 7 days as an indication of treatment seeking.
6. Willing to completely cease cigarette consumption and switch to an e-cig
7. Willing to attend regular visits over a 6week period (not planning to move, not planning extended vacation, no planned surgeries)
8. Able to read and write in English
9. Able to understand and consent to study procedures

3.2 Exclusion Criteria

1. Unstable or significant medical condition in the past 12 months (recent heart attack or some other heart conditions, stroke, severe angina including high blood pressure if systolic >159 mmHg or diastolic >99 mmHg observed during screening)
2. Severe immune system disorders (uncontrolled HIV/AIDS; unstable multiple sclerosis symptoms), respiratory diseases (exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis), or any medical disorder/medication that may affect participant safety or biomarker data

3. Women who are pregnant (verified by urine pregnancy test at baseline visit), trying to become pregnant, or nursing
4. Use of any non-cigarette nicotine delivery product (pipe, cigar, cigarillo, dip, chew, snus, hookah, e-cigs, strips, sticks) in the past 7 days
5. Use of an e-cig for 5 or more days in the past 28 days or any use in the past 7 days
6. Uncontrolled mental illness or substance abuse or inpatient treatment for these conditions in the past 6 months
7. History of a seizure disorder or had a seizure in the past 12 months
8. Currently or have ever taken medications prescribed to prevent seizures (such as Carbamazepine or Phenobarbital). Using seizure medications for off-label use (indications other than treatment for seizures) will not be included as an exclusion, these will be assessed on a case-by-case basis
9. Surgery (cardiac, thoracic, eye, ENT or abdominal) requiring general anesthesia in the past 6 weeks
10. Use of marijuana or any illicit drug/prescription drugs for non-medical use daily/almost daily or weekly in the past 3 months per NIDA Quick Screen
11. Use of hand-rolled, roll your own cigarettes
12. Known allergy to propylene glycol or vegetable glycerin
13. Other member of household currently participating in the study

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

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

3.3.1.1 Withdrawal prior to randomization

Participants who meet any criteria below at Visit 1 will be considered for withdrawal prior to randomization:

- Not smoking ≥35 cigarettes in past week
- Use of a non-cigarette nicotine delivery product in the past 7 days
- Reporting a quit attempt in the past 30 days
- Unable to provide a urine sample

3.3.1.2 General withdrawal criteria

Participants may be discontinued by the PI at any point during the study for any of the following reasons:

- **Missing their study visit window**: If a participant misses their study visit window, the participant will be considered for withdrawal from the study.
- **New pregnancy**: Participants who report a new pregnancy at any point during the study will be withdrawn.
- **Suicide attempt**: If at any time during the study it is discovered that a participant has made a suicide attempt, they will be withdrawn from the study.
- **Cardiovascular disease (CVD) event requiring inpatient hospitalization**: CVD typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new vavlular disease (e.g., mitral or aortic regurgitation).
- **DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system) requiring inpatient hospitalization**.

- **Adverse events related to e-cig use**: Adverse events will be monitored at every study visit.
- **Worsening substance abuse** in which the participant is behaving inappropriately at visits or demonstrates an inability to continue with the study.
- **Any inpatient hospitalization or debilitation** in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the site PI and medical professional to determine whether continued participation in the study is appropriate (this could include recovery from a major surgery, worsening of psychiatric symptoms, etc.).
- **Any situation where participant is not able to use their e-cig for a period of more than 2 weeks** (e.g., incarceration or other similar situation) unless they report non-study product use by choice.
- **Participant choice**: Participants may choose to remove themselves from the study by informing the research team in writing at any point during the study. If they choose to remove themselves from the study, they will not receive any further contact from the study center.
- **Inappropriate E-cig use:** If a participant reports at any time that they have tampered with their research e-cig device or liquid or they have shared the device with others, the PI can withdraw the participant at their discretion. Also, if a participant reports at any time that they have used e-cig products not purchased from reputable sources, including products containing THC, they will be withdrawn.
- **Participant behavior**: If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, appears/admits to giving away/selling study products, consistently loses study products etc., then the PI can withdraw him/her from the study at the PI's discretion.

3.3.2 Follow-up for withdrawn subjects

If participants are withdrawn from the study for any of the reasons noted above (in 3.3.1.1. or 3.3.1.2.) prior to randomization, they will be replaced until a total of 240 participants have been randomized to the study. Reasons for withdrawal will be ascertained from subjects who voluntarily withdraw from the study (End of Trial Form).

4.0 Recruitment Methods

4.1 Identification of subjects

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

4.2 Recruitment process

Interested volunteers calling the study center number will first complete the eligibility script and questions for IRB STUDY00002213. If a participant's responses match this study's specified inclusion criteria they will be forwarded to research staff for further screening.

4.3 Recruitment materials

Recruitment materials used are the materials used in STUDY00002213:

4.4 Eligibility/screening of subjects

1. **Screening 1 (Phone):** We will consider the screening process and eligibility questions in IRB STUDY00002213 as Screening 1. This process includes a brief phone screening to determine basic eligibility for any of our study center protocols. Then, participants will complete the screening for this study in two additional steps.

2. **Screening 2 (Phone):** Participants determined to be potentially eligible for the study will be contacted by researchers via phone, email, or text to complete additional screening. Those contacted via phone will complete the screening questions over the phone with the researcher, while those contacted by email or text will be provided a link to complete the screening questions online (https://redcap.ctsi.psu.edu/surveys/?s=TT37498THYA77JXK). A full script and screening questions, as well the email and text script, specific to this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

3. **Screening 3 (In person, Visit 1):** After a participant has met basic eligibility criteria over the phone, they will be scheduled to come into the study center where they will be re-screened (using Screener 2). If the participant's answers have changed from the phone screener (Screener 2) and they are no longer eligible, they will be informed that they cannot participate and they will be compensated for their travel via gift card ($15). If they remain eligible, they will be consented to the study and further screened for eligibility. See section 7.2 for further details.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

When participants attend their first in person assessment visit, they will have the study explained to them in detail, have the opportunity to ask questions, and then will be asked to sign the consent form. Participants will be given a signed copy of the form. This will take place in a private clinic room at the Penn State Clinical Research Center.

5.1.1.2 Coercion or Undue Influence during Consent

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

5.1.2 Waiver or alteration of the informed consent requirement

N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

An IRB-approved consent form will be used to document written consent. The participant will be given a copy of the signed consent. The participant's signed consent form will be uploaded into the participant's REDCap record.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

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

In addition, participants who are not eligible for the study, or those who begin the phone screener but are not interested in completing it after learning more about the study, will be asked if they would be interested in being contacted for future studies being conducted by our research team. They will be informed that by providing their name and phone number, they will be consenting to allow the study team to contact them in the future.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

N/A

5.3.2 Cognitively Impaired Adults

N/A

5.3.2.1 Capability of Providing Consent

N/A

5.3.2.2 Adults Unable To Consent

N/A

5.3.2.3 Assent of Adults Unable to Consent

N/A

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

N/A

5.3.3.1 Parental Permission

N/A

5.3.3.2 Assent of subjects who are not yet adults

N/A

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

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

Check all that apply:

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

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

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

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

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

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

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

6.2.1.1 Plan to protect PHI from improper use or disclosure
Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers
All study data will be retained indefinitely.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI
The phone screener (Screener 2) will be used to check eligibility criteria (date of birth), and when participants are screened, their contact information will be used to follow-up about scheduling and for appointment reminders. This requires that we have complete contact (name, phone number) information.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization
In order to screen the participants prior to inviting them into the study center, the investigators are conducting a phone screening to determine if the participants are likely to be eligible for the study.

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

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

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

7.0 Study Design and Procedures

7.1 Study Design

This is a two-arm parallel-group, randomized, double-blind, placebo-controlled study.

7.2 Study Procedures

7.2.1 Screening (Phone)

All participants will be screened over the phone to ensure potential eligibility for the study. Those potentially eligible will be scheduled an in-person visit. Subjects will be instructed to smoke their usual brand of cigarettes normally for the next 7 days, avoid using any other tobacco products, and to tally the number of cigarettes smoked per day.

7.2.2 Baseline (Consent/Randomization) Visit – Visit 1 [Day 0]

The following procedures will be completed in a private clinic space in the Clinical Research Center. Participants and researchers will be wearing appropriate PPE at all times, except for noted measures where the participant will need to remove their mask (when COVID protocols apply).

(Part A): Consent and Confirm Eligibility

7.2.2.1 Prior to informed consent procedures, participants will complete the same screening questions that were completed over the phone previously (Screener 2 via phone) to confirm eligibility (at Visit 1). Participants will be asked to provide, for visual inspection, a photo identification to verify their age. Provided identification must be valid (ie. not expired), contain a photograph, a birthdate, and the name must match that of the participant. If participant meets eligibility criteria assessed via screening at Visit 1, they will continue with Visit 1 and be asked to provide informed consent. Otherwise, the participant will be compensated for their travel to the visit, and the End of Trial Form will be completed.

7.2.2.2 The participant will be provided with information about the study, will have the opportunity to ask questions, and will provide written consent to participate in the study. Participants will be provided with a copy of the consent form.

7.2.2.3 The following measures will be completed:

7.2.2.3.1 Medical history will be documented. Those with any conditions listed as exclusion criteria will be excluded.

7.2.2.3.2 Concomitant medication history will be recorded to ensure that the participant is not taking any medications that would exclude them from the study.

7.2.2.3.3 The NIDA Quick Screen will be administered and participants indicating the use of prescription drugs for non-medical use/illicit drugs/marijuana daily/almost daily or weekly over the past 3 months will be excluded.

7.2.2.3.4 Researchers will complete a 7 day timeline follow-back procedure to describe their cigarette use over the past 7 days. This is to confirm that the participant smoked at least ≥35 in the past week, and no quit attempts have been reported. If any of these criteria have not been fulfilled, the participant will be excluded.

7.2.2.3.5 Use of other tobacco products in the past 7 days will be assessed via Other Tobacco Use form. If the participant has used any other tobacco product in the past 7 days, they will be excluded.

7.2.2.3.6 Participants will complete an exhaled carbon monoxide reading. Exhaled CO ≥6 ppm will be confirmed for inclusion in the study. Participants with a CO reading lower than 6 ppm will be excluded.

7.2.2.3.6.1 When COVID protocols apply: Because this test requires that the participant remove their mask, the researcher will exit the room for this measure and will instruct the participant to complete the measurement via the two-way mirror and intercom system. Upon completing the measurement, the participant will be asked to put on their mask, and a timer for 15 minutes will be set as a guide for when the researcher may re-enter the room.

7.2.2.3.7 The participant will exit the clinic room to have their blood pressure measured. This is done in the small nursing station immediately outside of the clinic room. Participants with a blood pressure of systolic >159 mmHg or diastolic >99 mmHg will be excluded from the study.

7.2.2.3.8 Then the participant will have their height and weight measured.

7.2.2.3.9 Participants will then be taken to the CRC bathroom and will be asked to provide a urine sample. Participants unable to provide a urine sample will be excluded from randomization.

7.2.2.3.9.1 Pregnancy exclusion will be confirmed through a urine test that will be self- administered by the participants when they come to this visit. Participants with confirmed pregnancy will be excluded.

7.2.2.4 The participant will then return to the clinic space. The researcher will remain outside the room to assess eligibility to continue with the study.

7.2.2.4.1 If participants don't meet the eligibility criteria, they will be withdrawn from the study. They will be compensated for travel. The end of trial form will be completed. Eligible participants will continue with the study.

(Part B): Completion of Baseline Measures/Randomization

7.2.2.5 The 10 minute holter EKG procedure will be performed in the clinic space.

7.2.2.5.1 When COVID protocols apply: This procedure will be completed once the clinic space is cleared for researcher entry (ie. 15 minutes after the CO measurement, measured using a timer).

7.2.2.6 Participants will then be randomized to a study group via REDCap.

7.2.2.7 Following randomization, participants will receive the assigned study product (SREC with 0 mg/ml nicotine liquid or SREC with 58 mg/ml nicotine liquid; researcher and subject are blind to the nicotine dose), which will be pre-prepared by the unblinded research staff.

7.2.2.7.1 Participants will be provided 2 rechargeable e-cig batteries, 1 wall adapter, 1 USB charger cord, a user manual, and a supply of pods, based on the participant's cigarette smoking (up to 22 pods). In a case where the participant will run out of pods, the participant will be able to come to the study to pick up an additional supply.

7.2.2.7.2 Research staff will then explain how to use the device.

7.2.2.7.3 Participants will be advised to cease all tobacco use and to start using their assigned e-cig product beginning the next morning.

7.2.2.7.4 Participants will be provided with smoking cessation resources that are available in the community, and they will be encouraged to use them. In

addition, participants will be given the document from the Centers for Disease Control and Prevention titled, "A Report of the Surgeon General: How Tobacco Smoke Causes Disease."

7.2.2.7.5

7.2.2.7.6 Participants will be instructed to complete daily diaries related to their study product and cigarette use (E-cigarette Daily Diary – includes place to record cigarette use as well). They will also be asked to return all used or unused e-cig pods at their next study visit.

7.2.2.7.7 Pulmonary Function Testing (PFTs) – PFTs will be conducted as described in the Time and Events Table at Visits 1, 2, and 3. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event. All adverse events will be documented and reviewed by the Medical Monitor within 5 business days. In cases where the medical monitor suspects that a participant may be having a respiratory adverse event related to the study, a pulmonologist (Dr. Bascom) will be consulted. The pulmonologist will make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study.

7.2.2.7.7.1 When COVID protocols apply: The researcher will then leave the clinic space to complete the pulmonary function test, as the participant will need to remove their mask for this test. This will be facilitated by a two-way mirror and an intercom system. The researcher will remain outside of the clinic space for 15 minutes following the completion of this test and will use a timer to ensure that this time restriction is met.

7.2.2.8 Upon completion of the PFT test, participants will be given the opportunity to use the SREC device and ask the researcher any questions about its use prior to leaving the visit. The researcher will use the two-way mirror and intercom system to answer any questions.

(Part C): Visit Wrap-Up

7.2.2.9 Participants will then be provided with instructions to complete additional measures via a home computer/smart phone (see table of measures). A link to the surveys in REDCap will be sent to the participant's email address or phone. Participants will be instructed to complete all questionnaires within 24 hours. Participants unable to complete the questionnaires at home via a computer/smart phone will be called by the researchers to complete the questionnaires.

7.2.2.10 As the participant leaves the clinic space, participants will be provided with the Greenphire ClinCard.

7.2.2.10.1 Once participants complete the additional questionnaires considered to be part of the visit (completed at home within 24 hours), they will be compensated for the visit. The funds will be automatically loaded onto the card.

7.2.2.10.2 Those who do not complete the visit by completing the at-home questionnaires (which includes an option to opt-out of answering) will only be compensated for travel.

7.2.3 Switching Phase –Phone Contact #1 (Day 7 ± 7 days) and Phone Contact #2 (Day 14 ± 7 days)

Note: While visit windows were extended to allow the participant flexibility, no visits (in person or phone), will occur on the same day.

During each phone contact, daily study product and cigarette use will be collected, adverse events or changes to concomitant medications will be documented, and participants will be asked to answer the measures indicated in the Time and Events Table. Participants will also be provided with advice/encouragement to remain abstinent from cigarettes. Participant's compensation for completing the phone call will be added to their gift card.

7.2.4 Switching Phase – Visit 2 (Day 21 ± 7 days)

The following procedures will be completed in a private clinic space in the Clinical Research Center. Participants and researchers will be wearing appropriate PPE at all times, except for noted measures where the participant will need to remove their mask (when COVID protocols apply).

Prior to the visit:

7.2.4.1 Participants will then be provided with instructions to complete measures via a home computer/smart phone (see table of measures). A link to the surveys in REDCap will be sent to the participant's email address or phone the day of the clinic visit. Participants will be instructed to complete all questionnaires within 24 hours. Participants unable to complete the questionnaires at home via a computer/smart phone will be called by the researchers to complete the questionnaires.

(Part A): Participant Check-In

7.2.4.2 The following measures will be completed:

- **7.2.4.2.1** Adverse events will be documented, and any concomitant medication changes will be recorded.
- **7.2.4.2.2** The cigarette and study product use diary will be collected by the researcher and entered into Daily Cigarette and E-cig Use Diary Log in Redcap.
- **7.2.4.2.3** Use of other tobacco products in the past 7 days will be assessed via the Other Tobacco Use form.
- **7.2.4.2.4** Participants will be encouraged to remain abstinent from cigarettes.
- **7.2.4.2.5** Participants will be instructed to complete daily diaries related to their study product and cigarette use (E-cigarette Daily Diary). They will also be asked to return all used and unused e-cig pods at their next study visit.
- **7.2.4.2.6** Participants will be provided with a supply of pods based on their usage.

(Part B): Completion of Biomeasures

7.2.4.3 The participant will then leave the clinic space to have their blood pressure and weight measured.

7.2.4.4 Participants will then be taken to the CRC bathroom and will be asked to provide a urine sample.

- **7.2.4.4.1** A pregnancy test will be completed for women of childbearing potential.
- **7.2.4.4.2** Participants will complete an exhaled carbon monoxide reading.
- **7.2.4.4.3** Pulmonary Function Testing (PFTs) – PFTs will be conducted as described in the Time and Events Table at Visits 1, 2, and 3. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event. All adverse events will be documented and reviewed by the Medical Monitor within 5 business days. In cases where the medical monitor suspects that a participant may be having a respiratory adverse event related to the study, a pulmonologist (Dr. Bascom) will be consulted. The pulmonologist will make any needed medical recommendations and a

determination regarding whether the participant is able to continue with the study.

7.2.4.4.3.1 When COVID protocols apply: The researcher will then leave the clinic space to complete the CO and pulmonary function test, as the participant will need to remove their mask for this test. This will be facilitated by a two-way mirror and an intercom system. The researcher will remain outside of the clinic space for 15 minutes following the completion of this test and will use a timer to ensure that this time restriction is met.

(Part C): Visit Wrap-Up

7.2.4.5 As participants are leaving the clinic space, they will be provided with new pods. Based on usage information collected during the past two weeks' phone calls, participants will be provided with a new supply of SREC pods as needed. Participants will be able to retain their unused pods from the previous visit.

7.2.4.6 Once participants complete the additional questionnaires (completed at home within 24 hours), they will be compensated for the visit. The funds will be automatically loaded onto the card.

7.2.4.6.1 Those who do not complete the visit by completing the at-home questionnaires (which includes an option to opt-out of answering) will only be compensated for travel.

7.2.5 Switching Phase – Phone Contact #3 (Day 28 ±7 days) and Phone Contact #4 (Day 35 ± 7 days)

During each phone contact, daily study product and cigarette use will be collected, adverse events or changes to concomitant medications will be documented, and participants will be asked to verbally answer the measures indicated in the Time and Events Table during the phone call. Participants' answers will be entered directly into REDCap by the researcher at the time of the call. Participants will also be provided with advice/encouragement to remain abstinent from cigarettes. Participant's compensation for completing the phone call will be added to their Greenphire ClinCard.

7.2.6 Switching Phase – Visit 3 (Day 42 -7/+14 days)

The following procedures will be completed in a private clinic space in the Clinical Research Center. Participants and researchers will be wearing appropriate PPE at all times, except for noted measures where the participant will need to remove their mask (when COVID protocols apply).

Prior to the visit:

7.2.6.1 Participants will be provided with instructions to complete measures via a home computer/smart phone (see table of measures). A link to the surveys in REDCap will be sent to the participant's email address or phone the day of the clinic visit. Participants will be instructed to complete all questionnaires within 24 hours. Participants unable to complete the questionnaires at home via a computer/smart phone will be called by the researchers to complete the questionnaires.

(Part A): Participant Check-In

7.2.6.2 The following measures will be completed:

7.2.6.2.1 Adverse events will be documented, and any concomitant medication changes will be recorded.

7.2.6.2.2 The cigarette and study product use diaries will be collected by the researcher and entered into the Daily Cigarette and E-cig Use Diary Log in Redcap. Participants will stop using the diaries at this point of the study forward.

7.2.6.2.3 Use of other tobacco will be assessed via the Other Tobacco Use form.

7.2.6.2.4 All used and unused e-cig pods will be collected by the researcher for review. Participants will then be able to retain some of the unused pods based on their usage.

7.2.6.2.5 Participants will be encouraged to remain abstinent from cigarettes.

7.2.6.2.6 Participants will also verbally be provided with information regarding how they can purchase their own e-cig devices and products, similar to the one used in the study. Participants will be instructed to purchase e-liquid from reputable companies and to not buy from unknown or illicit sources.

(Part B): Completion of Biomeasures

7.2.6.3 The participant will then leave the clinic space to have their blood pressure and weight measured.

7.2.6.4 Participants will then be taken to the CRC bathroom and will be asked to provide a urine sample.

7.2.6.4.1 A pregnancy test for women of child-bearing age will be completed.

7.2.6.5 The participants will return to the clinic space to completed the 10 minute Holter EKG.

7.2.6.6 Participants will complete an exhaled carbon monoxide reading.

7.2.6.7 Pulmonary Function Testing (PFTs) – PFTs will be conducted as described in the Time and Events Table at Visits 1, 2, and 3. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event. All adverse events will be documented and reviewed by the Medical Monitor within 5 business days. In cases where the medical monitor suspects that a participant may be having a respiratory adverse event related to the study, a pulmonologist (Dr. Bascom) will be consulted. The pulmonologist will make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study.

7.2.6.7.1 When COVID protocols apply: The researcher will then leave the clinic space to complete the CO and pulmonary function test, as the participant will need to remove their mask for this test. This will be facilitated by a two-way mirror and an intercom system. The researcher will remain outside of the clinic space for 15 minutes following the completion of this test and use a timer to ensure that the time restriction is met.

(Part C): Visit Wrap-Up

7.2.6.8 Once participants complete the additional questionnaires (completed at home within 24 hours), they will be compensated for the visit. The funds will be automatically loaded onto the card.

7.2.6.8.1 Those who do not complete the visit by completing the at-home questionnaires (which includes an option to opt-out of answering) will only be compensated for travel.

7.2.7 Follow-Up Phase – Phone Contact #5 (Day 70 ± 7 days)

During this follow-up phone contact, past 7 day study product and cigarette use will be collected via a 7 day timeline follow-back (TLFB) procedure (meaning that participants will be asked to recall their use from memory for the past 7 days), adverse events or changes to concomitant

medications will be documented, and participants will be asked to answer the measures indicated in the Time and Events Table.

7.2.8 Follow-up Phase – Interview Visit 4 (Day 70 + 60 days) (Optional study visit)

At consent, participants will be given the option to be considered to participate in an additional study procedure, a structured interview about their experiences using the e-cig device to stop smoking.

Participants who consent to the optional part of the study will be contacted by the researchers after completion of the study (after Visit Ph #5) to schedule an additional study visit to complete the interview. Only participants who complete the study (ie. Complete Ph #5) will be contacted.

Participants who are contacted and who agree to participate in the interview will be contacted to schedule an in-person visit at the study center. The interview will take place via ZOOM and will last approximately 30-60 minutes. Interview questions will be related to the participant's experience using the e-cig and attempting to switch completely from cigarettes. All interviews will be recorded and transcribed. In addition, participants will be asked to provide their past 7 day cigarette (via 7 day TLFB) and e-cigarette use.

- We plan to recruit 40 participants to complete the interview part of the study. We plan to recruit participants who met the following criteria:
- 8 participants who successfully switched and were randomized to the 0mg/ml group
- 12 participants who successfully switched and were randomized to the 58mg/ml group
- 8 participants who did not successfully switch and were randomized to the 0mg/ml group
- 12 participants who did not successfully switch and were randomized to the 58mg/ml group

Successfully switching for the interview part of the study will be defined by no cigarette use reported in the past 7 days reported at Visit 3 and Visit Ph #5 and a CO < 6ppm at Visit 3.

The first participants who meet the outlined criteria will be contacted by the researchers. We will continue to recruit participants for each category until all interviews for that category is completed. The interviews will be completed by blinded researchers but the management of the recruitment of participants for the interview will be managed by an unblinded study team member. This will ensure that recruitment for each category is correctly executed.

7.2.9 Follow-up Phase – Product Use Visit (Day 70 + 60 days) (Optional study visit)

At consent, participants will be given the option to be considered to participate in an additional study procedure. Participants who consent to the optional part of the study will be contacted by the researchers after completion of the study (after Visit Ph #5) to schedule the additional visit.

Participants who meet the following criteria will be contacted:
- Complete the study (ie. Complete Ph #5)
- Still using a nicotine containing product at Ph #5

The first participants who meet the outlined criteria will be contacted by the researchers. We will continue to recruit participants this optional visit until 10 participants have completed.

For the procedure, participants will be asked to use the SREC product in the lab while blood is collected. First, participants will be asked to abstain from any nicotine containing products for at least 14 hours before attending the visit. Once they arrive at the study center, a CO will be collected to verify abstinence (CO < 15 ppm to be eligible). Then, participants will complete

baseline questionnaires about withdrawal and craving. Then, participants will be given the SREC device with a 5% pod to use in the lab in a standard manner of 1 puff every 20 seconds for 14 puffs total (4 minutes, 20 seconds). Blood will be collected via an intravenous line at baseline and then 1, 2, 4, 6, 8, 10, 12 and 15 minutes after the first puff on the device. After the last sample is collected, the IV will be removed and participants will be asked to complete another CO measurement and to complete questionnaires about withdrawal and craving as well as questionnaires about their experience with the product.

Time and Events Table
X = measure completed remotely by participant

	Baseline Phase	Switching Phase							Follow-up Phase	
Study Week Number	0	1	2	3	4	5	6	10	10	10
Study Day	0	7	14	21	28	35	42	70	70	70
Study Visit Number	1	Ph #1	Ph #2	2	Ph #3	Ph #4	3	Ph #5	4 (ZOOM)	6
Measures/Questionnaires										
COVID screening questions (day prior to visit)	X			X			X			
Screening Questions	x									
Daily Cigarette and E-cig Use Diary	X	X	X	X	X	X	X			
Past 7 day Cig and E-cig use								X	X	
Other Tobacco Use	X	X	X	X	X	X	X	X		
E-cig Patterns of Use and Log		X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X		
Medical History	x									
Cigarette Details	x									
Adverse events	X	X	X	X	X	X	X	X		
Demographics (Including Social Determinants of Health (SDOH))	x									
Tobacco use history	x									
Importance/Confidence to Quit	X			X			X	X		
NIDA drug screener (past 3 months)	x									
Environmental tobacco smoke	X			X			X			
Cigarette/E-cig perceived health risk	X			X						
E-cig Perceived Benefits and Harms	X									
Cigarette and E-cig Liking and Evaluation scales	X			X			X	X		x
Study Product Side Effects questionnaire		X	X	X	X	X	X	X		x
Cigarette dependence (HONC, FTND, PSCDI)	X			X			X	X		
E-cig Dependence (Penn State E-cig DI)				X			X	X		
Questionnaire smoking urges	X	X	X	X	X	X	X	X		x
Minnesota withdrawal scale	X	X	X	X	X	X	X	X		x
Audit-C	x						X			
CES-D	X			X			X			
Kessler K6	X			X			X			
Perceived stress scale	X			X			X			

Clinical COPD questionnaire (CCQ)	X			X			X			
PROMIS Sleep Disturbance & Impact	x			X			X			
Interheart and WI Prepare	x						X			
Real World E-cig Use								X		
Interview									X	
Biomeasures/Procedures										
Weight	X			X			X			
Height	X									
Exhaled CO	X			X			X			x
Blood pressure/pulse	X			X			X			
Pulmonary function test (FEV1, FVC, PEF, FEF25, FEF75, FEF25-75, FET)	X			X			X			
Urine sample (NNAL, CYMA, MHBMA3, 3HPMA,8-isoprostanes, creatinine, cotinine)	X			X			X			
Holter EKG test (10 minutes)	X						X			
Pregnancy test	x			X			X			
Product use procedure										x

7.2.10 Daily Cigarette Diary and Daily E-cig Diary

During the entire study period (not including the follow-up phase), participants will be required to record the number of cigarettes smoked per day and study product use (after randomization) on provided paper-based diaries. Participants will be given an E-cigarette Daily Diary that also includes a space to record any cigarettes smoked. Researchers will enter daily diary totals in REDCap at each study contact for all days in the study. Daily diaries will stop after Visit 3 and participants will only be asked about past 7 day use at subsequent visits.

7.2.11 Unscheduled Visits

If a participant requires additional study product (e.g., e-cig pods), or if the SREC product fails, they may call the research center to schedule a time to obtain additional products (in-person). Product may also be shipped to the participant's home if they are not able to come to the study center in a timely manner.

7.2.12 Appointment Reminders

Phone call and/or text message reminders will be used throughout the study to remind participants of their next visits (approximately 1-2 days prior). In addition, when COVID protocols apply, participants will be sent a link to their phone or email to complete COVID symptom screener 24 hours before the visit. Also, visit time/date confirmation and study center directions will be emailed to the participant prior to Visit 1. (SEE APPOINTMENT REMINDER LETTER ATTACHMENT). For those without email, the first visit instructions will be explained to the participant over the phone. For participants who allow us to contact them through phone and text messaging, the study team will be using Google Voice to call or text participant reminders of the study visit and reminders to complete the study surveys with the REDCap survey link. Google Voice is phone service that allows researchers to communicate with participants without revealing their personal phone numbers. The study team will save participants phone number with their study ID. Participants will be told not to share PHI through this phone number.

7.2.13 Biospecimen Processing

All urine samples collected will be analyzed in the research lab. These samples will be analyzed for NNAL, CYMA, MHBMA3, 3HPMA, creatinine, 8-isoprostanes, and cotinine.

7.2.14 Data Collection via Phone

If participants are unable to attend an in-person study visit, the researcher will attempt to collect data over the phone. Participants will not be compensated for data provided through this method.

7.2.15 Missed Visit Procedures

Participants will be called at least once to reschedule a missed Visit 1. For participants who do not show up for in-person Visits 2-3, up to 3 phone/text/email attempts will be made to contact them to reschedule their appointment. After the 3rd attempt, a letter will be emailed to the address on file informing them that the study team has been trying to reach them and asking them to contact the study center to reschedule. No further attempts to contact the participant will be made after the letter is sent (see study documents for letter).

7.3 Duration of Participation

Participants who complete all phases of the study will participate in the study for a total of 10 weeks.

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

7.4.1 Description

The e-cig used will be a Standardized Research E-Cig (SREC). The SREC product is a pod-based device and comprises a replaceable pre-filled liquid reservoir ("pod") and a rechargeable power supply unit. The SREC was designed for reliability and user convenience. Important features include: breath actuation, a tank and battery of sufficient capacity to satisfy smokers for >1 day on a single unit, primary packaging of the tank with excellent oxygen and water vapor barrier properties to ensure a long shelf life, and power control to maintain a constant aerosol output over the lifetime of the tank and battery charge. Preliminary pharmacokinetic data on the SREC with 58 mg/ml nicotine liquid suggests that 5 minutes of puffing (10 puffs) produces a C_{max} of just over 21 ng/ml at around 5 minutes, and preliminary studies of subsequent ad-lib use suggest blood nicotine levels around 15 ng/ml. Both the 58 mg/ml (5%) and 0 mg/ml (0%) nicotine pods contain 1.9 ml of liquid, 50:50 propylene glycol: glycerin based with a tobacco flavor.

7.4.2 Treatment Regimen

Participants will be randomized to receive either a 0 mg/ml or 58 mg/ml nicotine liquid to be used with the SREC device. They will be told to use the SREC ad libitum as a replacement for conventional cigarette use.

7.4.3 Method for Assigning Subject to Treatment Groups

Participants will be randomized to one of two conditions: a SREC with pods containing 0 mg/ml nicotine content (placebo) or a SREC with pods containing 58 mg/ml nicotine content (nicotine). Using a 1:1 allocation ratio, the randomization template was created by the study's unblinded statistician via blocked randomization. The Randomization Module in REDCap will assign each participant to a 6-digit alpha-numeric code upon randomization at Visit 1. This code is unique to each randomized participant and is accessible to all study personnel. This code provides a blinded reference which identifies the SREC-device kit to be assigned and associated with the pharmacy device distribution. The utilization of this alpha-numeric code allows study personnel to be blinded from the nicotine dose while simultaneously distributing the devices to the

participants. The master blinded randomization file links each alpha-numeric code to a randomized nicotine dose. This file does not exist in REDCap, is not stored on any shared accessible network drives, and is not accessible to any blinded study personnel (except in the event of an emergency situation that requires the breaking of the blind).

In the event that REDCap is down during a Visit 1 and a participant is ready to be randomized, the REDCap Randomization downtime procedure should be followed and implemented. This means that pharmacy will continue their list and no data will be entered into REDCap until participant can be randomized in the system.

7.4.4 Subject Compliance Monitoring

Participants will be given daily diaries to complete on which they will record the number of cigarettes smoked and number of e-cig puffs each day. Participants will be given detailed instructions on how to complete the logs. Questions will be asked at each contact to review participants' logs and to verify their daily conventional cigarette and e-cig use. Participants will also be asked to self-report their other tobacco use including products such as cigars, pipes, chew, snus, dip, hookah, and dissolvable tobacco. Exhaled carbon monoxide measurements and urine samples will be collected throughout the study to verify smoking intensity, nicotine, and cotinine levels.

Participants will be asked to return all of their used and unused study products and to bring their e-cigs to the study visits following randomization. At each of these visits, study staff will review the used pods to get an estimate of how much e-cig liquid was used by the participant.

7.4.5 Blinding of the Test Article

The SREC products will be received by unblinded staff. The pods will contain a barcode, which will be scanned by the unblinded staff to determine the numeric code. The unblinded staff will match the numeric code on the pod to a list linking the numeric code with the allocation, active (58 mg/ml) or placebo (0 mg/ml).

Unblinded staff will appropriately package the pods and SREC parts into packs/kits for the participants. The kits will have assigned numbers, and the participants will be randomly assigned to a kit number at the randomization visit (Visit 2). The blinded researcher will not be involved in the packing and labelling of the kits and will only have access/knowledge of the alpha-numeric kit code assigned – but will remain blinded to the dose that each kit corresponds to. Only the study statisticians and packing/labeling personnel will be unblinded to the dose that each kit is linked to via randomization. All other study personnel, including lab staff, will remain blinded until the last randomized participant completes Phone Call #5 in the study follow-up phase at Week 10.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The SREC device will be purchased from NJOY, LLC in its standard packaging and shipped to Penn State and will be received by unblinded staff. Pre-filled, sealed, disposable pods containing 1.9 mL of e-cig liquid will also be purchased from NJOY. The pods will come in blister packs containing 2 pods.

7.4.6.2 Storage

All study products (e.g., SREC devices, pods) and components will be stored in TCORS space in a locked closet in Room H7514 away from light, heat, and moisture.

7.4.6.3 Preparation and Dispensing

The pods will come pre-filled in individually sealed packages. They will be prepared for participants by unblinded staff and stored with unique identifiers. Unblinded staff will appropriately package kits containing two SREC devices and a supply of filled pods for the participants. At Visit 1, following confirmation of eligibility for randomization, participants will be randomly assigned a kit number. The blinded researchers will not be involved in the packing and labeling of the kits.

All receiving, sorting, blinding, and dispensing of the study product will be done in the TCORS pharmacy space at Penn State in Room H7514.

7.4.6.4 Return or Destruction of the Test Article

Participants will be dispose of their SREC device and all used and unused pods after completion of Phone Contact #5or if they are withdrawn. The devices provided to participants in this study are not commercially available and thus cannot be used without the pods provided in the study.

7.4.6.5 Prior and Concomitant Therapy

Concomitant medication use will be collected regularly throughout the trial and to monitor participant health conditions.

Participants taking varenicline, bupropion or nortriptyline as a smoking cessation medication in the prior month will be excluded from the study. Participants taking bupropion or nortriptyline for depression management and who expect to continue use of the medication throughout the trial will be eligible to participate. Additionally, participants who are prescribed bupropion or nortriptyline for depression management at any point during the study will be eligible to continue with the study. Medications related to certain medical conditions that are exclusions to the study, such as COPD and current heart conditions, will serve to alert the study staff of the presence of these conditions during screening. Once the participant is entered into the randomized double blind phase of the study, there are no medications that will interfere with the participant's ability to participate.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Participants will be enrolled in the study until a total of 240 are randomized. We anticipate that we will need to enroll up to 300 participants in order to randomize 240.

8.2 Sample size determination

We plan to randomize a total of 240 participants (120 in each dose group), and it is assumed that, although all efforts will be made to ensure 100% retention in the trial, as many as 30% of participants may drop-out after randomization. Thus, the effective sample size for this study could be as low as 84 per group, as the primary study endpoint is measured and collected at the last in-person study Visit 4.

Therefore, n=84 is the expected number of participants in each group to complete Visit 4 (e.g. complete the 'Switching Phase' of the study). It is expected that the NNAL levels in the nicotine-containing e-cigs group will be similar to results obtained by Goniewicz et al[13] assuming a pre-treatment mean =225ng/ml creatinine (SD 165) vs. post-treatment 80 ng/ml creatinine (SD=69). The pre-treatment values of the placebo e-cigs group are expected to be similar to that of the nicotine-containing e-cigs group, as this measure occurs prior to randomization. The n=84 per group sample size should enable us to detect a post-treatment NNAL difference of 35 ng/ml creatinine or larger between groups (i.e., the placebo e-cigs group's post-treatment NNAL mean value be > 115), with at least 90% statistical power under 5% type 1 error.

8.3 Statistical methods

For the analysis, the baseline time will be Visit 1, prior to randomization to an e-cig nicotine content regimen (placebo or nicotine), which occurs at end of Visit 1.

Summary statistics will be provided for baseline smoking characteristics, along with other study demographics collected upon enrollment/screening at Visit 1. Summary statistics will also be provided for all variables at each visit. This will include all randomized subjects.

Aim 1: For each battery of measures, the mean change from week 1 to week 6 will be estimated with a corresponding 95% confidence interval. The p-value for testing zero underlying change will also be provided. This analysis will be conducted separately for the two treatment arms. To adjust for multiple comparisons, the false discovery approach will be used. Additionally, the trajectory of each measurement at visit 1 visit 2 and visit 3 will be modeled using linear mixed effects regression.

Aim 2: The difference between the two treatment arms on markers of health risk will be analyzed. The primary conceptual framework is a modified intent-to-treat: subjects will be analyzed by their randomized arm regardless of compliance with the e-cig nicotine content regimen, as long as data for the particular outcome is available at either of the post-randomization visits (Visit 2 or Visit 3). The basic statistical tool will be linear regression or logistic regression. Two sets of regressions will be conducted. The first set of regressions will model the dependence of the outcome measures at week 6 on the two treatment arms while controlling for the baseline value of the outcome variable. The second set of regressions will adjust for additional covariates at baseline (V1), to be selected via backward elimination at 0.05 significance level. These additional covariates will be chosen from the following list based on appropriateness for the specific outcome variable.

- Age
- Race
- Hispanic
- Education status
- Gender
- Income
- SDOH questionnaire (ACES score)
- Baseline cpd
- Baseline CO
- Baseline NNAL
- Baseline cotinine
- Menthol/non-menthol cigarettes
- Cigarette length
- Height
- Weight
- BMI

- Baseline FEV1
- Baseline PSCDI
- Quit attempt history
- "Currently, do you have any symptoms or a disease that you believe is caused or made worse by your tobacco use?" (yes/no)
- Perceived cessation support questions
- ETS questionnaire
- Baseline MNWS
- Baseline QSU
- Baseline audit – c
- Baseline cigarette perceived health rick score
- E-cig Perceived risk/Perceptions of e-cig risks (from screener)
- Baseline CESD
- Baseline Kessler 6
- Baseline perceived stress
- Baseline COPD questionnaire
- Baseline interheart
- Importance and confidence to quit

Same strategy will be used for withdrawal items on the MNWS and scores on ratings of cigarette craving. The analysis will be conducted for the values of these variables at week 3, however.

Cigarette Abstainers Subgroup Analysis
In addition to the intent-to-treat analysis, additional analysis on subgroup of regular cigarette abstainers only will be conducted. By design, this subgroup will only consist of Switching Phase Completers (still in the study at the time of V3) who have successfully abstained from cigarette and other tobacco use (except e-cigs) from 1 week prior to V2 consistently and consecutively until V3. Therefore, this subgroup would be defined as 'quit' for at least 4 weeks. Participants in this sub-group must also have an exhaled CO < 6 ppm at both V2 and V3. Based on our previous data, we believe that 40% of the nicotine e-cig group (84 x .40 = roughly 33 participants) and 20% of the placebo e-cig group (84 x .20 = roughly 16 participants) will be classified as abstainers. For this relatively small subgroup, we shall only model the dependence of the outcome measures at week 6 on the two treatment arms while controlling for the baseline value of the outcome variable. No elaborate adjustment of other covariates will be included.

Aim 3: The proportions of subjects who will try to abstain from cigarettes and who will continue to use an e-cig at week 10 will be compared between the two arms using Fisher's exact test. Switching Phase dropouts will be treated as 'non-abstainers' from cigarettes under the 'worst case-scenario' assumption. A supplementary logistic regression will also be conducted to explore their dependence on demographic variables in addition to the two treatment arms.

Multiple imputation for missing values
We will strive to minimize the number of missing values by rigorous follow-up with the study subjects. In spite of this, we still anticipate some missing values in the final datasets. Our basic tool to address this problem is multiple imputations. More specifically, if a variable is missing at V1, it will be imputed from the distribution of that variable of non-missing subjects. Due to the randomization at V1, non-missing subjects from both arms will be used for the distribution. For values missing at V3 (6 weeks after randomization), but non-missing at V2, the value collected at V2 will be carried forward in time via the LOCF (Last Observation Carried Forward) approach. For any instance where the participant remained in the trial, but did not provide data values at either post-randomization visit (V2 or V3), that case will be excluded from the analysis (modified ITT).

For some scenario, the missing values can be imputed by some reasonable assumptions. If a participant dropped out of the study prior to Visit 3 without providing Visit 2 data for the outcome, a 'worst-case-scenario' assumption will be made – assuming that the participant reverted back to exclusive smoking of cigarettes upon dropping out of the trial. Under this assumption, their Visit 2 baseline value will be carried forward to Visit 3. See the table below for a detailed outline of these methods:

Stratified Imputation Approach:

V1	V2	V3	V` Baseline Result	V3 Endpoint Result	Mechanism of Missing
+	+	+	Use directly	Use directly	N/A
+	+	-	Use directly	Impute V3 via LOCF from V2	Dropped out between V2 and V3
					Missing V3 due to item non-response
+	-	+	Use directly	Use directly	N/A
-	+	+	Impute the V2 value from the overall sample distribution	Use directly	N/A
+	-	-	Use directly	Impute V3 via LOCF from V1	Dropped out between V1 and V2 Assume 'Worst-Case-Scenario'
			Excluded from Analysis (Modified ITT)		Dropped out between V2 and V3 Item Non-Response at V2
			Excluded from Analysis (Modified ITT)		Completed the Switching Phase Missing V2 and V3 due to item non-response
-	+	-	Impute the V1 value from the overall sample distribution	Impute V3 via LOCF from V2	Dropped out between V2 and V3
					Missing V3 due to item non-response
-	-	+	Impute the V1 value from the overall sample distribution	Use directly	N/A
-	-	-	Excluded from Analysis (Modified ITT)		

(+) = non-missing data
(-) = missing data

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form.

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

See the Research Data Plan Review Form.

9.1.1.1 Use of Codes, Master List

See the Research Data Plan Review Form.

9.1.2 Storage of Data and/or Specimens

See the Research Data Plan Review Form.

9.1.3 Access to Data and/or Specimens

See the Research Data Plan Review Form.

9.1.4 Transferring Data and/or Specimens

N/A

9.2 Subject Privacy

See the Research Data Plan Review Form.

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The study coordinator and the PI will be responsible for the oversight of subject safety. Patients will be under medical supervision while in the study (i.e., by the medical monitor) and seen on an ongoing basis by our research staff who will document adverse events. The medical monitor (Dr. Sciamanna) will assess adverse events and will consult with the pulmonologist on respiratory adverse events. The PI and/or the medical monitor will meet weekly with the study staff to review patient's progress and their experiences with the study products, including any adverse events. Entrance criteria will be reviewed following screening. Medical history will be reviewed by the study staff, and based on eligibility criteria, any questionable medical histories will be brought to the attention of the medical monitor for final inclusion determination prior to randomization. In a similar manner, contraindications for the treatment products and vital signs will be checked by study staff at each in person visit. The medical monitor will be available via phone for any consultations as necessary. In addition, the study coordinator/statistician will prepare a cumulative report of all data points listed below for the Data and Safety Monitoring Committee to review every 6 months after recruitment begins.

10.2 Data that are reviewed

The Data and Safety Monitoring Report will include:

- Accrual and retention
- Medical history and concomitant medications
- Adverse events and serious adverse events
- Protocol deviations/violations
- Misconduct
- Conflict of interest
- Participants' ability to achieve study requirements
- Changes in lung function via pulmonary function testing
- Changes in lung function via the Clinical COPD questionnaire

10.3 Method of collection of safety information

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

10.4 Frequency of data collection

Safety data, including adverse events and serious adverse events will be collected at each in-person visit.

10.5 Individuals reviewing the data

The study coordinator and the PI will be responsible for the oversight of subject safety. The PI and the medical monitor will meet weekly with the study staff to review patient's progress and their experiences with the study products, including any adverse events. For more urgent and/or serious adverse events, the medical monitor will be available for consultation by phone. The medical monitor will then make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study. For respiratory adverse events, the pulmonologist will be available for consultation. The DMSB will review the reports every 6 months.

10.6 Frequency of review of cumulative data

Safety data will be reviewed cumulatively based on recommendations from the DSMB. They will receive summary reports every six months and convene at least annually.

10.7 Statistical tests

There are no planned interim statistical analyses for this study. Statistical summaries and reports for all enrolled study participants will be generated for periodic DSMB Review. Reports will include summarized data and information pertaining to participant recruitment and accrual, study retention-dropout rate (withdrawals, lost to follow up, Switching Phase completion, Trial completion), (serious) adverse events, pulmonary function, and any other safety data requested by the DSMB (such as blood pressure, heart rate, weight, CO increases, etc.). The DSMB will meet to determine the desired format for the reports and the requested content (e.g. individual-level data, aggregate summary data, etc.). The data presented/reported will not be summarized by treatment group, thus allowing the reviews to occur in a blinded fashion for the DSMB, the PI, the study team, and the statisticians generating the reports.

10.8 Suspension of research

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

11.0 Risks

11.1 E-cig use: There may be some unknown risks related to the use of e-cigs.

11.1.1 The most common side effects associated with using an e-cig are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, nasal congestion, sore throat, mouth ulcers, rash, dizziness, difficulty breathing, heart palpitations, abnormal heart rate, headache, stomach discomfort, chest pain, nausea, vomiting, and hiccups.

11.1.2 E-cig liquid contains vegetable glycerin, propylene glycol, and flavorings. It is possible that participants may have an allergy to one of 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.

11.1.3 There are reports that some people who use e-cigarettes have experienced seizures, with most involving youth or young adult users. Participants with a history of seizures or take medications to prevent seizures will be excluded from the study.

11.1.4 There have been some reports of serious lung illnesses among those who used e-cigarettes, and even some cases of death as a result. The cause of all these 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 e-cigarette products that contained tetrahydrocannabinol (THC) and/or products that were bought off the street and not from retail establishments. The e-cigarette products used in this study do not contain THC and were bought from manufacturers where

quality testing and control is performed. Nonetheless, participants will be advised to call their doctor immediately if they experience cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, or fever after using their e-cigarette. Participants will be told to only use the e-cigarette and liquid pods (cartridges) given to them by the researchers and to not tamper with their e-cigarette or use other liquids with the e-cigarette device.

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

11.3 **Nicotine withdrawal symptoms:** Ceasing conventional cigarette use may result in nicotine withdrawal symptoms (e.g., irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, difficulty concentrating). These symptoms will be monitored at each visit.

11.4 **New development of pregnant or want to become pregnant:** Nicotine, from cigarettes and from e-cigs, 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. Females capable of becoming pregnant will be administered a pregnancy test prior to beginning the research. Participants must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation.

11.5 **Spirometry:** Risks associated with spirometry may include shortness of breath, dizziness, headache and on rare occasions fainting while doing the breathing test. Every effort will be made to limit these effects during the procedure. Participants with medical conditions that may place them at increased risk are being excluded.

11.6 **Holter EKG test:** There is little risk associated with a Holter EKG, however, discomfort may include minor skin irritation or localized allergic skin reaction. These reactions typically subside after removal of the monitor electrodes.

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

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

11.9 **Questionnaires:** It is possible that some of the questions in the questionnaires may make participants uncomfortable. They will be instructed that they are free to skip any questions that make them uncomfortable. In addition, at Visit 1, participants will be provided with a handout listing local, state and national resources for those who may want to seek out additional support (see Community Resources document).

11.10 (Optional Visit Only) **Blood Draws:** Blood draws often cause mild pain, swelling or bleeding. There may be some bruising (blood under the surface of the skin), which will be minimized by pressing on the site after the needle is removed. There is a slight chance that a blood clot will develop at the site of the catheter. There is also a slight chance of infection (less than 1 in 10,000), dizziness, or fainting. These risks will be minimized and most likely eliminated by having trained staff draw blood in a clinical setting using sterile supplies. If dizziness or fainting occurs, the symptoms will be alleviated by having you lie flat with your feet raised.

11.11

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no guaranteed direct benefit to the individuals who participate in this study. However, those who participate and who are able to switch successfully to the e-cig may have less exposure to tobacco-related toxicants as a result of their participation. In addition, they may reduce their dependence on traditional cigarettes.

12.2 Potential Benefits to Others

Society as a whole will benefit from the research because it is expected to provide important information on tobacco related health markers and the effects of switching to e- cigs on smokers.

13.0 Sharing Results with Subjects

This study is not designed to diagnose any disease or condition. However, if during the course of conducting clinical procedures (e.g., blood pressure, lung function), a participant is found to have a result outside of clinical norms, the result will be discussed with the participant (blood pressure, lung function, EKG result). The participant will be given a letter at the next visit indicating what procedure was done and will direct them to contact a medical provider for further evaluation. If a woman tests positive for pregnancy, the results will be shared with the participant, they will be withdrawn from the study, and they will be advised to follow up with their doctor for prenatal medical care. If at any time participants request copies spirometry results, they will be provided with copies of these and informed that they are not diagnostic tests. After the trial has completed, participants will be sent a letter providing them with their study condition.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Total compensation for study completion is $150 ($165 if completing optional part of the study). Actual payment will vary according to the number and type of contacts completed by each subject.

The payment will be provided by Greensphire Clincard. This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. The participant will be issued a ClinCard, which is a debit card that funds are loaded onto and can be used at the participant's discretion. The research team will give Greenphire some personal information about the participant, as described below. Greenphire will only use the personal information to process this reimbursement and will not share it with anyone for any other purpose. If the card is lost, the participant may be responsible for the replacement fee. When the visit is completed, funds will be approved and loaded onto the card. The funds will be available within 2-3 business days. In order to assign a ClinCard and load funds onto the ClinCard, Greenphire will need the Study/Subject ID, participant's name, Address, and date of birth. The participant will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send these messages Greenphire, the participant will need to provide their Mobile Phone Number and/or E-mail Address.

14.1 In-Person Visits (1, 2, 3)

- Subjects will receive a $15 gift card at each in-person visit to cover travel expenses.
- In addition, subjects will receive an additional $15 gift card upon completion of each study visit including the at-home questionnaires
- Subjects who complete all three in-person study visits will receive an extra incentive of $35 upon completion of Visit 3.

14.2 Phone Contacts

Compensation for each completed phone call will be $5, payable by a cumulative lump sum on the Greenphire ClinCard upon completion of Phone Contact #5. The actual amount of this sum will be determined by how many phone calls are completed. The total for completing all 5 phone calls in the study will be $25, upon completion of Phone Contact #5. If a participant did not complete any phone calls during the study, or if they did not complete Phone Contact #5, they will not receive any of the potential $25 compensation.

14.3 Optional Visits

Participants who complete the optional phone interview will be compensated $15. Participants who complete the optional study product use visit will receive $15 for travel and $45 for visit completion.

		Visit and Payments Table								
Study Week Number	0	1	2	3	4	5	6	10	10	10
Study Day	1	7	14	21	28	35	42	70	70	70
Study Visit Number	1	Ph #1	Ph #2	3	Ph #3	Ph #4	3	Ph #5	Optional Interview	Optional Study Product Use
Payments **Transportation** **Visit Completion** **TOTAL**	$15 +$15 $30	Potential $5	Potential $5	$15 +$15 $30	Potential $5	Potential $5	$15 +$15 $30 + $35 if all clinic visits complete	Potential $5 + sum of phone call payments (up to $25)	$15	$15 + $45 $60

15.0 Economic Burden to Subjects

15.1 Costs

There will be no costs to the subjects for any of the procedures or tests associated with the study. Participants will be provided with a study product at no cost. Participants and/or their insurance companies will not be responsible for costs related to study procedures and tests.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

All participant visits will take place in the Penn State Hershey Clinical Research Center.

16.2 Feasibility of recruiting the required number of subjects

The smoking prevalence in South Central Pennsylvania is 19% of the adult population. Our recruitment strategy is designed to broadly disseminate information about the study to members of the community.

16.3 PI Time devoted to conducting the research

Dr. Foulds has no clinical responsibilities and so the majority of his time is devoted to research, including this project. He is funded at 10% time for this study.

16.4 Availability of medical or psychological resources

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

16.5 Process for informing Study Team

Regular team meetings will be conducted where study procedures, questions, and issues will be discussed and resolved.

17.0 Other Approvals

17.1 Other Approvals from External Entities

The FDA will require submission of an Investigational Tobacco Product (ITP) application. A Certificate of Confidentiality has also been obtained.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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 – Hershey 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 on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ 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 – Hershey 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 on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

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

18.0 Multi-Site Research

18.1 Communication Plans
N/A

18.2 Data Submission and Security Plan
N/A

18.3 Subject Enrollment
N/A

18.4 Reporting of Adverse Events and New Information
N/A

18.5 Audit and Monitoring Plans
N/A

19.0 Adverse Event Reporting

19.1 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	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical

Unexpected suspected adverse reaction.	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.
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.

19.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at in-person study visits and during scheduled phone contacts.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study 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.

In addition, we will be monitoring lung function throughout the study using pulmonary function testing. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event.

19.3 Causality and Severity Assessments

The medical monitor (Dr. Sciamanna) will review documented adverse events and abnormal test findings on a weekly basis 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. For more urgent and/or serious adverse events, the medical monitor will be available for consultation by phone or immediate medical attention will be sought (ie. Emergency room). The medical monitor will then make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study. In cases where the medical monitor suspects that a participant may be having a respiratory adverse event related to the study, a pulmonologist (Dr. Bascom) will be consulted. The pulmonologist will make any needed medical recommendations and a determination regarding whether the participant is able to continue with the study.

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

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports

N/A

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

N/A

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

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

19.6 Unblinding Procedures

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

19.7 Stopping Rules

There are no planned interim statistical analyses or stopping rule assessments for this study due to the low risk of the intervention. The DSMB will convene and notify the study team if they believe at any point, upon review of the safety data presented in the DSMB reports, that certain risks to subjects inflicted by continuing in the study outweigh the likely benefits of study completion. A brief report will be generated from each of the DSMB meetings for the study record and will be forwarded to the Institute's Institutional Review Board (IRB).

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control

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

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

defined in an iterative self-documenting process by all members of the research team. This iterative development and testing process results in a well-planned data collection strategy for individual studies.

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

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

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

20.1.2 Safety Monitoring

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

The research coordinator will ensure that AEs are correctly entered into REDCap and complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

21.0 Future Undetermined Research: Data and Specimen Banking

Blood and urine will be banked for future undetermined research for all participants. Before samples are used or shared, the participant's identity we will be removed.

21.1 Data and/or specimens being stored

Specimens will be stored with an ID code attached. The location of the specimen in the study freezer will be managed using Freezerworks database which will be housed on the PHS password secured network. The code number, visit number, date/time of collection, processing and storage, and consent options for future use of samples will be stored in Freezerworks in addition to REDCap. All other data associated with the ID code will be retained in REDCap.

21.2 Location of storage

Specimens will be stored a locked freezer room in the research laboratory of Drs. Muscat & Foulds on the 3rd floor of the Cancer Institute.

21.3 Duration of storage

Specimens will be stored indefinitely with code number attached. Data will be stored indefinitely with identifiers attached in REDCap and no identifiers in Freezerworks.

21.4 Access to 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 to forms (i.e., researchers who see participants will not have access to data that may allow them to become unblinded to a participant's treatment allocation).

21.5 Procedures to release data or specimens

Investigators who are interested in obtaining samples from this project for ancillary studies will first be required to submit a detailed written proposal to Dr. Foulds. Dr. Foulds will then take the proposal to the overall Penn State Tobacco Center of Regulatory Science (TCORS) steering committee for review and approval. If the proposal is approved, the investigator will then need to obtain all other regulatory approvals (IRB, departmental scientific committees, etc.) prior to samples being released. Only de-identified data, as approved in the investigator's IRB application, will be released to the investigator. Blood and urine samples will only be released if the participant provided written consent to allow their samples to be used by other investigators (this option is included in the original consent form).

21.6 Process for returning results

Investigators will be required to provide a written report on their study results to the TCORS steering committee. Individual participants will not be provided with the results of the analyses of their samples.

22.0 References

1. U. S. Department of Health and Human Services. *The Health Consequences of Smoking - 50 Years of Progress: A Report of the Surgeon General.* Atlanta, US: U.S: Department of Health and Human Services, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;2014.
2. U. S. Department of Health and Human Services. *The Health Benefits of Smoking Cessation: A Report of the Surgeon General.* Atlanta: U.S: Department of Health and Human Services, Centers for Disease Control and Prevention, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health;1990.
3. Schoenborn CA, Gindi RM. Electronic Cigarette Use Among Adults: United States, 2014. *NCHS Data Brief.* 2015(217):1-8.
4. 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):385-390.
5. 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;65:92-97.
6. 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.
7. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term Pulmonary Effects of Using an Electronic Cigarette: Impact on Respiratory Flow Resistance, Impedance, and Exhaled Nitric Oxide. *Chest.* 2012;141(6):1400-1406.
8. Cibella F, Campagna D, Caponnetto P, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin. Sci.* 2016;130(21):1929-1937.
9. Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC Cardiovasc. Disord.* 2014;14(1):78.
10. Farsalinos K, Cibella F, Caponnetto P, et al. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Intern. Emerg. Med.* 2016;11:85-94.
11. Manzoli L, Flacco ME, Ferrante M, et al. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. *Tob. Control.* 2017;26(3):284-292.

12. Manzoli L, Flacco ME, Fiore M, et al. Electronic Cigarettes Efficacy and Safety at 12 Months: Cohort Study. *PLoS One.* 2015;10(6):e0129443.
13. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob IIIP, Benowitz NL. Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. *Nicotine & Tobacco Research.* 2017;19(2):160-167.