PennState

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

Protocol Title:
Randomized trial of low nicotine cigarettes plus electronic cigarettes in smokers

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1.0 Objectives

1.1 Study Objectives

The long term goal of this project is to determine the likely health effects of very low nicotine content in cigarettes, in conjunction with availability of nicotine-containing electronic cigarettes (e-cigs) among smokers with mental health conditions (SMHC). This will be tested in a rigorous randomized controlled trial design. We plan to use a comprehensive set of measures of proven validity and reproducibility, including toxicant exposure, addiction and mental health to assess these effects. The specific objective of this study is to recruit a cohort of 240 current exclusive daily SMHC (diagnosed using the MINI International Neuropsychiatric Interview) and to measure a comprehensive battery of behavioral and health indicators at 4 and 8, 12 and 16 weeks after being randomized to use either normal nicotine content (NNC) Spectrum cigarettes (11.6 mg nicotine/cigarette) or very low nicotine content (VLNC) Spectrum cigarettes (0.2 mg nicotine/cigarette) while also having access to a JUUL e-cig (JUUL Labs, Inc.) containing either 0% or 5% nicotine strength e-liquids in a randomized double-blind, placebo-controlled 2 by 2 design. Our central hypothesis is that key markers of harms to health (e.g. urinary NNAL, exhaled CO, measures of addiction, and mental distress) will be significantly improved among SMHC who are provided very low nicotine cigarettes and high nicotine e-cigs. Study aims are:

Aim 1: To determine whether SMHC have lower levels of markers of harm (e.g. urine NNAL, exhaled CO, measures of mental health) and cigarette addiction when switched to VLNC cigarettes, as compared with NNC cigarettes, at the end of the randomized phase (week 16).

Aim 2: To determine whether SMHC have lower levels of markers of harm (urine NNAL, exhaled CO) and cigarette addiction when provided with nicotine-containing versus zero nicotine electronic cigarettes, at the end of the randomized phase (week 16).

Aim 3: To determine whether use of VLNC cigarettes increases the proportion of smokers who completely switch away from combustible tobacco use (no cigarette use in the past 7 days and CO < 6ppm), as assessed (a) at the end of the randomized phase (week 16) and (b) 4 weeks after the end of the randomized phase of the trial (week 20), compared to those using NNC cigarettes.

1.2 Primary Study Endpoints

The primary endpoint for the study is urinary NNAL concentration at Week 16. Urine NNAL is a biomarker that provides an accurate estimate of recent exposure to the lung carcinogen, NNK.

1.3 Secondary Study Endpoints

Secondary endpoints include exhaled CO, Kessler-6 score, and cigarette/e-cigarette dependence using Penn State Cigarette Dependence Index (PSCDI) and Penn State Electronic Cigarette Dependence Index (PSECDI), at week 16, and cigarette abstinence (no cigarette use in the past 7 days and CO < 6ppm) at week 20.

Additional endpoints include:
Health effects and toxicant exposure measures: Pulmonary Function Tests (PFT), Clinical COPD Questionnaire (CCQ), urinary CYMA (biomarker for acrylonitrile [volatile organic compound] exposure), 3HPMA (biomarker for acrolein [volatile organic compound] exposure, cotinine (biomarker of nicotine exposure)

Mental health measures: Center for Epidemiological Studies-Depression (CES-D), Overall Anxiety Severity and Impairment Scale (OASIS), Quick Inventory or Depressive Symptomatology (QIDS), Perceived Stress Scale (PSS)
Nicotine/Tobacco use and addiction measures: daily cigarette use, daily e-cig use, Fagerstrom Test for Nicotine Dependence (FTND), Hooked on Nicotine Checklist (HONC), , Minnesota Nicotine Withdrawal Scale (MNWS)

2.0 Background

2.1 Scientific Background and Gaps

Tobacco use remains the single biggest cause of preventable morbidity and mortality in the United States,(1) and cigarettes are by far the most commonly used tobacco product. For example, among all adults in the PATH Wave1 survey, 16% were daily users of cigarettes with the next most commonly used product being smokeless tobacco, at 1.8% of adults using daily.(2) A product standard for combustible tobacco products that limits the permissible nicotine content to a level that significantly reduces their addictiveness has the potential to significantly reduce the harms to public health from tobacco use in the United States.(3-5) The Family Smoking Prevention and Tobacco Control Act gave the FDA jurisdiction to implement such a product standard for cigarettes and other combustible tobacco products. The primary rationale for reducing the permissible nicotine content is to minimize the uptake and addictive use of cigarettes by new cohorts of young people.(6, 7) At the very least such a policy should not do harm to current smokers, particularly to vulnerable populations. A number of studies of reduced nicotine content cigarettes have now taken place and we have recently completed our own trials.(5, 8-10) However, very few trials to date have provided evidence on two key questions where gaps in our scientific knowledge remain. First, we do not know what the effects may be of immediate (as opposed to gradual) switching to VLNC cigarettes in SMHC. Second, when switching to VLNC cigarettes, no investigations have been conducted in a more realistic manner that enables systematic study of the effects of access to e-cigs. This trial will be significant and innovative as it will be the first ever randomized controlled trial to provide evidence of immediate switching to VLNC cigarettes in SMHCs while systematically studying the impact of access to e-cigs.

It has long been recognized that adults with mental health conditions are much more likely to smoke cigarettes than those without mental health conditions. Over time, those with mental health conditions are comprising a larger proportion of the remaining smokers.(11) For example, the current smoking prevalence among people without serious psychological distress fell from 20% in 2005 to 14% in 2015, whereas among people with serious psychological distress it stayed the same (42% vs. 41%) and actually increased for men.(12) The high smoking rates among people with mental health conditions is an important reason for large health disparities between people with serious mental health problems and those without, particularly in life expectancy.(13) Recent studies suggest that people with mental health conditions are similarly more likely to try, and to continue to use, e-cigs.(14, 15) For FDA to implement a reduced nicotine standard for combusted tobacco products it must possess reliable scientific data to estimate the likely public health effects in the real-world context of e-cig availability. In particular, FDA will need to know the health and addiction effects on SMHC. The proposed study will provide the data for this growing segment of the smoking population.

Over the past 10 years, e-cigs have become increasingly popular in the U.S. where more than 79% of U.S. adults are currently aware of the devices and 3.7% are using one on a regular basis.(16) Current every-day or someday e-cig use is most prevalent among current smokers (15.9%) and recent ex-smokers (22.0%) and is very uncommon among adult never cigarette smokers (0.4%).(16-18) E-cigs are battery-powered devices that heat and vaporize a liquid mixture (e-liquid), typically containing a vehicle such as propylene glycol (PG) and/or vegetable glycerin (VG) and often, but not always, nicotine and/or flavorings, to produce an aerosol that is inhaled by the user. E-cigs can expose users to several chemicals known to have adverse health effects including nicotine, carbonyls, and volatile organic compounds

(VOCs). The health effects of heated and aerosolized constituents of e-cig liquids, including solvents, flavors, and toxicants, are not completely understood.(19) However, some studies suggest e-cigs, when used exclusively, have a more favorable toxicity profile than tobacco cigarettes.(20, 21) E-cigs have become increasingly popular among cigarette smokers, particularly SMHC. For example, in the PATH Wave 1 survey, cigarettes plus e-cigs was by far the most common pattern of combined use.(2) In a large population survey from 2015, people with a mental health condition were twice as likely to be current cigarette smokers and twice as likely to be current e-cig users as people without a mental health condition.(14) This study aims to assess the likely health effects of a product standard lowering the nicotine content of cigarettes in SMHC when having access to e-cigs.

It is highly likely that in a scenario in which FDA issued a product standard requiring only very low nicotine content in cigarettes, existing smokers may attempt to supplement their nicotine from alternative sources. Given the current prevalence of e-cig use among current and former smokers, they are a prime candidate for such a source. To date, most studies designed to evaluate the likely effects of a low nicotine product standard for cigarettes have required participants to only use the specially designed reduced nicotine content cigarettes without supplementation from their own cigarettes or any other nicotine sources.(4, 8) This was a reasonable research design, however it has become clear that a significant proportion of those allocated to smoke only VLNC cigarettes were non-compliant, as their cotinine concentrations could not realistically be obtained from smoking only VLNC cigarettes.(22, 23) It seems most likely that the participants "topped off" their nicotine levels by occasionally smoking normal nicotine cigarettes. In the real world, if a product standard requiring only VLNC in cigarettes were to be implemented it is likely that alternate nicotine products, such as e-cigs, would also be available, so it is important to examine the patterns of product use and the resulting effects on biomarkers of toxicant exposure in that situation.

An initial feasibility trial of the reduced nicotine standard randomized smokers to 8 weeks of either NNC cigarettes or VLNC cigarettes and provided participants with access to alternative nicotine sources (either a variety of non-combusted products or a variety that included combusted products).(24) In this study, e-cigs were the most commonly selected alternative nicotine products used in all groups, and those allocated to VLNC cigarettes used more alternative products, had greater reductions in smoking rates and greater reductions in NNAL and exhaled CO compared with NNC cigarettes.(24) These results support the presumption that a reduced nicotine standard for cigarettes will likely lead to increased use of e-cigs and suggests that access to non-combusted nicotine products may enhance the effects of VLNC cigarettes leading to reduced smoking and toxicant exposure. The Donny and Hatsukami research group (CENIC) is currently preparing to implement two funded trials of reduced nicotine cigarettes in the context of alternative nicotine availability. However, there are no such trials focusing on the effects of VLNC cigarettes on smoking behavior and toxicant exposure specifically among SMHC, a vulnerable population that requires specialized investigations focused on how nicotine reduction may impact their mental health and smoking behavior. The current trial is designed to provide this much needed evidence.

2.2 Previous Data

Below, we summarize key relevant findings from our team's recent research, which leads to both our interest and expertise in conducting this proposed study.

Research on Reduced Nicotine Content Cigarettes. In our recently completed trial, participants were randomly assigned to smoke either (a) NNC cigarettes (11.6 mg/cig); or b) Reduced Nicotine Content (RNC) cigarettes where the nicotine content per cigarette is progressively reduced to 0.2 mg/cig in five steps over 18 weeks. Participants were then offered the choice to either (a) quit smoking with assistance, (b) continue smoking the research cigarettes, or (c) return to their own cigarettes, and were followed up for a further 12 weeks. After controlling for the baseline measure, plasma cotinine, exhaled CO and FTND score were all significantly lower at the end of randomized phase in the RNC group as

compared to the NNC group. Measures of nicotine dependence (mean cigarettes smoked per day, Penn State Cigarette Dependence Index) were significantly lower at the end of the randomized phase in the RNC group, as compared to the NNC group ($p<0.003$), whereas measures of psychiatric problems (CES-D depression score, QIDS depression score, OASIS anxiety score and MNWS nicotine withdrawal score) showed no significant change in the RNC group as compared to the NNC group. Analyses focusing on those participants who were compliant with exclusive use of research cigarettes throughout the randomized phase of the trial (in the RNC group having a reduction in mean cotinine from 245 ng/ml at visit 4 to 8 ng/ml at visit 10), found an almost identical pattern of results to the randomized phase completer analysis.

Treatment Choice: At the end of the randomized phase all participants were given the choice of (a) quit smoking with assistance, (b) continue smoking the research cigarettes, or (c) return to their own cigarettes, before being followed up for a further 12 weeks. At the end of the treatment choice phase and the whole trial (12 weeks later), the RNC group was more likely to have quit smoking (18% [17/94] vs. 4% [4/94], $p=0.004$), based on intent-to-treat analysis including all 188 randomized participants, and validated by exhaled CO<9ppm. This study found that gradual switching to RNC cigarettes reduced dependence and toxicant exposure and enhanced smoking cessation. In addition, there was no evidence that gradual switching may cause harms to the mental health of smokers with mood or anxiety disorders.

Research on E-cigs. Our research on e-cigs has highlighted the important differences between different types of e-cig devices and liquids.(25) We have found that very few long term e-cig users continue to use the most popular starter “cig-a-like” brands that are approximately the same size and shape as a regular cigarette, as most either stop using e-cigs or transition to an advanced device characterized by a larger battery and a manual button.(26) Our survey studies suggested that continued use of an advanced generation e-cig device is at least partly driven by nicotine delivery (e.g., 77% switched to their current device in order to obtain a “more satisfying hit”).(26)

Both our NIH-funded Tobacco Center of Regulatory Science grant (P50-DA-036107) and our collaboration with the Virginia Commonwealth University TCORS (P50-DA-036105) have enabled us to explore new approaches for assessing the toxicity and addictive effects of electronic and tobacco cigarettes. For example, we used electron paramagnetic resonance spectroscopy (EPR) to measure free radicals in aerosols from different e-cigs, liquids, and “dry puffing”. The results demonstrated, for the first time, the production of highly oxidizing free radicals from e-cigs which may present a potential cardiopulmonary risk to e-cig users.(27) We have also undertaken laboratory studies comparing the nicotine absorption in experienced e-cig users using their own brands/liquids, with that of experienced cigarette smokers. We have published on the brain fMRI effects of the e-cigs,(28, 29) and perhaps the most significant result from these studies was the marked variability in nicotine absorption from different e-cigs, despite the fact that all were regular daily users using e-cigs with a nicotine concentration in the liquid of at least 12 mg/ml, and all used a standardized puffing protocol (30 puffs over 10 minutes). Results found some participants obtained cigarette-like nicotine absorption, others obtained almost no increase in blood nicotine level.

When we analyzed the nicotine absorption by a-priori e-cig type categorizations it was clear that cigarette smokers obtained more consistently high and rapid nicotine absorption. Users of advanced e-cigs also obtained significantly higher nicotine absorption than users of first generation or “cig-a-like” brands, who absorbed minimal nicotine. These laboratory results are consistent with our survey results, demonstrating that e-cig users are likely to gravitate toward devices with characteristics that result in more efficient and rapid nicotine absorption (such as a larger more powerful battery). Our team has also developed a new questionnaire to measure dependence on e-cigs. In a collaborative study with Yale and other TCORS on 1,009 e-cig users, the 10-item Penn State *Electronic* Cigarette Dependence Index (PSECDI) correlated +0.7 with a new e-cig version of the 22-item PROMIS Nicotine Dependence

items.(30) In addition, in a large sample of current exclusive e-cig users recruited online (n=3609), we have used the PSECDI to demonstrate that regular e-cig users are less dependent on e-cigs than they retrospectively report having been on cigarettes prior to switching.(31) Recently, we replicated a similar pattern of results based on analysis of a comparison of nicotine dependence among exclusive daily e-cig users and exclusive daily cigarette smokers identified in a nationally representative sample recruited to the Wave 1 of the PATH study.(32)

In a collaborative TCORS project, we were one of two sites in a large randomized controlled trial to examine the effects of e-cigs on toxicant exposure. Along with Virginia Commonwealth University,(33) this trial involves recruiting 520 smokers interested in reducing their smoking (not quitting) and randomizing to one of 4 conditions (a cigarette substitute, or an e-cig containing 0, 8 or 36 mg/ml nicotine liquid) including 12 visits over 9 months. The Penn State site has exceeded original recruitment targets and recruited 320 of the overall planned 520 participants in that trial. The trial includes a number of health risk measures, including NNAL (primary outcome), expired air carbon monoxide (CO), nicotine (via its metabolite cotinine in urine), biochemical and hematologic health indices such as C-reactive protein (CRP), pulmonary function (via spirometry), and biomarkers of oxidative stress (e.g. glutathione). Main outcome results are currently being analyzed.

2.3 Study Rationale

We believe that a product standard restricting the permissible nicotine content for cigarettes and other combustible products offers major potential public health benefits both by reducing cigarette uptake in future generations of young people and by reducing dependence, cigarette consumption and therefore toxicant exposure among existing smokers. However, the effects of an immediate significant drop in cigarette nicotine content needs to be studied in SMHC because of their increased dependence on nicotine and vulnerability to nicotine withdrawal. In addition, the potential impact of e-cig availability in response to a reduced nicotine standard also needs to be evaluated due to the increasingly widespread use of e-cigs and their potential health effects. We believe that by using a double-blind randomized-trial design with long term (16 weeks) access to both research cigarettes and e-cigs, and comprehensive biomarker measurement in smokers with a variety of current and recent mental disorders, we will be able to thoroughly assess the effects of switching to VLNC cigarettes in this vulnerable population in a more comprehensive manner than has previously been achieved. The outcomes of this novel project will directly inform FDA on the feasibility of a low nicotine standard for cigarettes in SMHC.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Ages of 21–70
2. Smoke $\geq$5 cigarettes per day for at least the prior 12 months
3. Smoke regular, filtered cigarettes or machine rolled cigarettes with a filter
4. Exhaled CO measurement of $\geq$ 6 parts per million at baseline
5. No serious cigarette smoking quit attempt or use of any FDA-approved smoking cessation medication in the prior 30 days (includes any nicotine replacement, varenicline, bupropion [used specifically as a quitting aid])
6. No plans to quit smoking within the next 3 weeks
7. History of a mental health condition like depression, anxiety, panic attacks, ADHD, schizophrenia, an eating disorder, or any other mental health condition and/or have a past history of receiving treatment, counseling or medication for a mental health condition

8. Must be willing to both switch to a different type of cigarette that may contain a different amount of nicotine and to try an e-cig to substitute for some of their cigarettes
9. Must be willing and able to respond to contacts from study staff or attend visits over the study period (not planning to move, not planning extended vacation, no planned surgeries)
10. Must meet lifetime diagnostic criteria for a current or lifetime unipolar or bipolar mood disorder (e.g. major depressive disorder, major depressive episode, manic episode, hypomanic episode, bipolar disorder), an anxiety disorder (e.g. panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, , agoraphobia, social anxiety disorder, generalized anxiety disorder), a psychotic disorder (e.g. mood disorder or other psychotic disorder), or an eating disorder (e.g. anorexia or bulimia) based on the MINI-International Neuropsychiatric Interview Standard (version 7.0.2).(34)
11. Able to read and write in English
12. Able to understand and give informed consent
13. Access to a computer/smartphone with e-mail and a reliable internet connection

3.2 Exclusion Criteria

1. Women who are pregnant and/or nursing or trying to become pregnant
2. Unstable or significant medical condition in the past 3 months (e.g., recent heart attack or other serious heart condition, stroke, severe angina)
3. High blood pressure (systolic >159 mmHg or diastolic >99 mmHg during screening)
4. Respiratory diseases (e.g., exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (e.g., dialysis) or liver disease (e.g., cirrhosis), severe immune system disorders (e.g., uncontrolled HIV/AIDS, multiple sclerosis symptoms) or any medical disorder/medication that may affect participant safety or biomarker data
5. Uncontrolled mental illness or substance abuse, or inpatient treatment for these in the past 6 months
6. Use of any non-cigarette nicotine delivery product (e.g., pipe, cigar, dip, chew, snus, hookah, e-cig, strips or sticks, IQOS) in the past 7 days at screening
7. Use of an e-cig for 5 or more days in the past 28 days or any use in the past 7 days at screening
8. Use of marijuana for non-medical use or other illegal drugs/prescription drugs for non-medical use daily/almost daily or weekly in the past 3 months per NIDA Quick Screen
9. Use of medical marijuana that is smoked (combusted) or use of recreational (illegal) THC vaping products
10. Any known allergy to propylene glycol or vegetable glycerin
11. Surgery requiring general anesthesia in the past 6 weeks
12. Unwilling to remain on one flavor of cigarette (regular or menthol) for the duration of the trial
13. Previous use of SPECTRUM research cigarettes in the past 6 months
14. Other member of household currently participating in the study
15. History of a seizure disorder or had a seizure in the past 12 months
16. Currently taking or have taken medications prescribed to prevent seizures (such as Carbamazepine or Phenobarbital). Using seizure medications for off-label use (indications other than treatment for seizures) will not be included as an exclusion, these will be assessed on a case-by-case basis

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

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

Criteria for withdrawal prior to randomization

- **Participant reports using non-cigarette nicotine products at Visit 2 AND Visit 3.** Includes cigars, pipes, snuff, chew, hookah, electronic cigarette, marijuana, IQOS, or any other illegal smoked substance, or any other nicotine containing product.
- **Participant's total cigarette consumption includes more than 10% of non-research cigarettes at Visit 3**
- **Participant has reduced their cigarette consumption by more than 50% compared to baseline (Visit 1) cigarettes per day (CPD) at Visit 2 or Visit 3.** This does not include situations of illness or other circumstances that would interfere with the participants' normal smoking behavior.
- **Participant must have smoked a total of 25 or more cigarettes in the past 6 days at Visit 2 and Visit 3.** This does not include situations of illness or other circumstances that would interfere with the participants' normal smoking behavior.
- **Reporting a quit attempt**

These circumstances of withdrawal may be taken on a case-by-case basis and actual withdrawal of the participant will be decided by the researcher. For example, continuation in the study may be possible if the participant has acted in good faith during the study.

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

- **Missing their randomization visit:** If a participant misses Visit 3, 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. (Except Visit 7; Note: no study products will be provided to the participant at Visit 7)
- **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 valvular 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.**
- **Elevated blood pressure at any visit (systolic >159 mmHg or diastolic >99 mmHg).**
- **Adverse events related to e-cig use:** Adverse events will be monitored at every study visit.
- **Significant smoking rate increase compared to baseline:** A participant will be withdrawn from the study if they meet BOTH of the following criteria (any visit prior to Visit 7):
    - The average cigarette per day (CPD) increase by more than 100% from the average CPD at Visit 1
    - The average of two consecutive expired breath carbon monoxide measurements increase according to the following:
        - CO is greater than 50 ppm if CO at Visit 1 is <20 ppm.
        - CO is greater than 60 ppm if CO at Visit 1 is 20 – 34 ppm.
        - CO is greater than 70 ppm if CO at Visit 1 is 35 – 49 ppm.
        - CO is greater than 80 ppm if CO at Visit 1 is 50 – 60 ppm.

- CO is greater than 90 ppm if CO at Visit 1 is 61 – 70 ppm.
- CO is greater than 100 ppm if CO at Visit 1 is 71-80 ppm.
- CO is greater than 110 ppm if CO at Visit 1 is 81-90 ppm.
- CO is greater than 120 ppm if CO at Visit 1 is 91-100 ppm.

- **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.).
- **Use of recreational (illegal) THC products that are vaped.**
- **Participant choice:** Participants may choose to remove themselves from the study by informing the research team verbally or in writing at any point during the study.
- **Participant behavior:** If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, appears/admits to giving away/selling study products, consistently loses study products etc., then the PI can withdraw him/her from the study at the PI's discretion.

3.3.2 Follow-up for withdrawn subjects

If participants are withdrawn from the study for any of the reasons noted above prior to randomization, they will be replaced until a total of 240 participants have been randomized to the study. Subjects who withdraw themselves or are withdrawn from the study at a visit will be asked to complete the study visit including a questionnaire regarding the reasons for dropping out.

For participants who withdraw themselves from the study, they will be asked if we can follow up with them at the week 16 visit. We will contact them via one call, message, and letter to complete the week 16 visit. If they wish not to be contacted to complete the week 16 visit, they will not be contacted.

If participants are lost to follow-up (i.e. simply do not respond to calls or letters without formally withdrawing) one final attempt will be made to contact them for the week 16 visit via one call, message and letter. If they complete the week 16 visit they will also be invited to the final (week 20) visit.

4.0 Recruitment Methods

4.1 Identification of subjects

Recruitment for this study will be facilitated through IRB STUDY00002213 (Study name: Call Routing Screener) which will also serve as the initial recruitment point of contact. We will also use Studyfinder to identify participants. Studyfinder is a web-based recruitment tool for Penn State researchers, managed and sponsored by Penn State Clinical Translational Science Institute (CTSI). The study team is enrolling subjects with mental health disorders.

This study will also identify subjects through the Penn State Health electronic medical record. Penn State EIM will release a data report of patients who have been diagnosed with nicotine dependence and

either depression or generalized anxiety. Only those who have had a patient visit in the past 3 years will be included. The report will include patient contact information (i.e. phone number, email address, and address). Researchers will reach out to potential participants through these avenues to let them know about the study opportunity.

4.2 Recruitment process

The methods of recruitment for this study are included in IRB STUDY00002213 in addition to Studyfinder. Interested volunteers will call the study center number (or fill out the survey online) to 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. In addition, if a participant matches this study's specified inclusion criteria from the questions in IRB STUDY00002213, they will be emailed a recruitment message with details about this study (see recruitment email uploaded under Recruitment Materials). Researchers will also identify potential participants from the EIM data report generated from the EMR.

The coordinator will attempt to call a participant for screening into this study. If the coordinator cannot connect with the participant through phone, they will follow up the phone call with a text message. The text message will state the researcher's purpose of the phone call and if the participant is interested in hearing details about the study, they can text the phone number back with a convenient time for the coordinator to call. The purpose of the text message is to determine the best time to contact participants based on their schedule.

4.2.1 How potential subjects will be recruited.

Recruitment for this study will be facilitated through IRB STUDY00002213. Details on how participants will be recruited and recruitment materials are in IRB STUDY00002213. Our study details will also be listed on Studyfinder. Participants who qualify for this study that are recruited through IRB STUDY00002213 will receive a recruitment email message with details of this study.

4.2.2 Where potential subjects will be recruited.

Recruitment for this study will be facilitated through IRB STUDY00002213. Details on where participants will be recruited are in IRB STUDY00002213. Potential participants will also be recruited through Penn State's Studyfinder website (studyfinder.psu.edu).

4.2.3 When potential subjects will be recruited.

Recruitment for this study will be facilitated through IRB STUDY00002213. Details on when participants will be recruited are in IRB STUDY00002213. While enrollment is open, details of the study will be listed on Studyfinder.

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

1. **Call Routing Screener in IRB STUDY00002213 (Phone or online survey):** We will consider the screening process and eligibility questions in IRB STUDY00002213 as Screening #1. This process includes a brief phone or online survey screening to determine basic eligibility for any of our study center protocols. Based on their answers to the questions participants will

be routed to this study. Then, participants will complete the screening for this study in two additional steps.

2. **Project Screener 1 (Phone, Email, Text):** Participants will be contacted by researchers via phone, email, or text to complete the Project Screener 1. 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 REDCap link to complete the screening questions online on their own . A full script and screening questions specific to this study are in the "Consent Forms and Recruitment Materials" section of the IRB application. If a participant has met basic eligibility criteria, they will be scheduled to come into the study center for their first visit.

   The data collected from screening will be kept to understand reasons why people cannot participate. Data may be used for future research. All data will be de-identified before future use.

3. **Project Screener 2 (In person at Visit 1):** At Visit 1 they will be re-screened using Screener 1. If the participant's answers have changed from the phone screener (Screener 1) and they are no longer eligible, they will be informed that they cannot participate. If they remain eligible, they will be consented to the study and further screened for eligibility. A full script and screening questions are uploaded in the "Consent Forms and Recruitment Materials" section of the IRB application.

5.0 Consent Process and Documentation

5.1 Consent Process:

Check all applicable boxes below:

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

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

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

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

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

When participants attend Visit 1, 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. This will take place in a private clinic room at the Penn State Clinical Research Center.

Procedures during COVID-19:

We will use the verbal consent obtained during the Phone Screener 1 for the Remote Visit 1 procedures. At the in-person Visit 2 we will collect written consent. 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. This will take place in a private clinic room at the Penn State Clinical Research Center.

5.2.2 Coercion or Undue Influence during Consent

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

5.3 Waiver of Written Documentation of Consent

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

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

OR

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

OR

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

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

For participants determined to be eligible, a study visit will be made where they will complete a written consent form.

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

A verbal phone script will be used to inform potential subjects about the research and is uploaded in the Screener 1 document under Local Site Documents Question 2.

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

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

5.4.6 Debriefing

N/A

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

5.5.5 Additional pertinent information after participation

N/A

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

N/A

5.6.2 Cognitively Impaired Adults

5.6.2.1 Capability of Providing Consent

N/A

5.6.2.2 Adults Unable to Consent

N/A

5.6.2.3 Assent of Adults Unable to Consent

N/A

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

5.6.3.1 Parental Permission

N/A

5.6.3.2 Assent of subjects who are not yet adults

N/A

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

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

Check all that apply:

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

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

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

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

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

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

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

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the Research Data Plan Review Form

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

Screener 1 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, address) 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 screen to determine if the participants are likely to be eligible for the study.

Procedures during COVID-19: In order to minimize in person face-to-face participant contact we are conducting Visit 1 study procedures remotely (Remote Visit 1) and written consent is not obtainable until in-person Visit 2.

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

We propose to conduct a parallel-group, randomized, double-blind, 2-by-2 controlled trial in which 240 current SMHC will be randomized to one of 4 groups: 1) normal nicotine content cigarettes (NNCs) and nicotine containing e-cigs; 2) NNCs and zero nicotine e-cigs; 3) very low nicotine content cigarettes (VLNCs) and nicotine containing e-cigs 4) VLNCs and zero nicotine e-cigs.

After baseline phases on own cigarettes (one week) and NNCs (2 weeks), participants will be randomized to one of these four groups and will attend visits every 4 weeks for 16 weeks, at which point the main study outcome measures will be assessed. All participants will be followed up with a study visit 4 weeks after the final randomized visit to identify whether they have continued to use e-cigs/cigarettes and to assess their motivation in smoking abstinence.

7.2 Study Procedures

All study visits will occur in a private clinic room in the Penn State Clinical Research Center.

Procedures during COVID-19:
Visits 1, 6, and 8 will be done remotely either over Penn State Health Zoom or over the telephone. Questionnaires will be administered via e-mailed or texted link to REDCap, and completed on the participant's own computer/cell-phone, with their answers securely saved in REDCap. All other study visits will occur in a private clinic room in the Penn State Clinical Research Center.

Once in-person research is allowed again, the study will return to previously approved procedures.

Based on the restrictions set by the Dean (Participant mask removal must PAUSE for all observational studies at the College of Medicine), the study team will no longer perform exhaled CO or PFT tests during visits. With this modification there will be no need for participants to take off their mask during study visits. Once the restrictions are lifted, the study team will go back to collecting these samples during the study visit.

Visit 1 (Week -3)

During Visit 1, participants will be screened in person using Screener 2. They will be asked to provide photo ID to verify the age given in Screener 2. If the participant meets eligibility using Screener 2 they will be asked to provide informed consent. Informed consent will be obtained by research staff. During this process, the usual discussion of procedure, risks, side effects, confidentiality, voluntary participation, and right to refuse participation without prejudice will be explained to the participant. Participants must be capable of understanding the nature of this

study, its potential risks, discomforts and benefits before signing consent. Participants will receive a signed copy of the form.

Once the informed consent is obtained the following information will be collected to determine the final eligibility in accordance with inclusion/exclusion criteria mentioned above:

1. Measure exhaled CO
2. Obtain urine sample for pregnancy determination for women of child-bearing potential (those who have had a period in the past 12 months) and who have not had a hysterectomy
3. Obtain medical and concomitant medication histories
4. NIDA Drug Screener
5. Measure vital signs (blood pressure and heart rate)
6. Administer all modules in the Mini International Neuropsychiatric Interview (MINI) and current suicide risk assessment (see MINI Standard (version 7.0.2) document). Researchers will administer the MINI mental health diagnostic tool electronically through the nView Health online application. **Procedure for suicide risk at screening:** If a participant scores ≥9 on the MINI suicide module the Psychiatric Medical Monitor (Dr. Ahmad Hameed) will be contacted. The researcher will discuss the score with the Psychiatric Medical Monitor and they will determine if the participant's enrollment into study is appropriate.

If a participant does not meet eligibility they will be compensated for their travel.

If a participant meets all the eligibility criteria they will be asked to complete questionnaires via an electronic survey in REDCap or administered by a study coordinator. See Table 1 for questionnaires and biomeasures collected at this visit. Participants will be given a laptop with access only to the internet and an individualized REDCap survey will be opened so they can complete direct data entry. The study staff will review the study guidelines and provide participants with instructions on how to keep track of the number of their usual brand cigarettes smoked each day for one week by using a cigarette log. All participants will be asked to refrain from using non-study tobacco/nicotine products or other smoked products during the study, but are encouraged to report the use of these products to the study staff. The next study visit will be scheduled for one week later. Participants will receive a print out of their upcoming study contacts and visits. Participants will be compensated for completing the study visit and procedures.

Table 1: Time and events schedule with measures, questionnaires, and biomarkers

Phase	**Baseline**			**Randomized**					**Follow up**
Study Visit Number	**1**	**2**	**3**	**Phone**	**4**	**5**	**6**	**7**	**8**
Study Week Number	**-3**	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**
Measures/Questionnaires									
Study and Non-Study Product Use									
E-cig and Cigarette Use log		X	X	X	X	X	X	X	X
Cigarette liking scales (35)			X		X			X	
E-cig Patterns of Use, E-cig Side Effects, E-cig Evaluation, E-cig Dependence (PSECDI),					X	X	X	X	X
E-cig Perceived Health Risk Rating					X			X	X
E- cig details									X
Basic participant and smoking characteristics									
Demographics (including Social Determinates of Health [SDOH])	X								
Tobacco use history, cigarette details	X								
Medical History	X								

NIDA Drug Use (36)	X							X	
AUDIT-C(37, 38)	X							X	
Environmental tobacco smoke questionnaire (39)		X							
Cigarette Perceived Health Risk		X	X		X			X	
Nicotine dependence (FTND, HONC, PSCDI (31, 40, 41))		X	X		X	X	X	X	X
Nicotine Use Disorder		X						X	
PROMIS Dependence		X						X	
Minnesota Nicotine Withdrawal Scale (42)		X	X		X	X	X	X	X
Questionnaire of Smoking Urges (QSU) (43, 44)		X	X		X	X	X	X	
Confidence to Quit								X	X
Mental Health and Wellbeing									
MINI International Neuropsychiatric Interview (MINI) (34)	X								
Kessler K6 scale (45, 46)		X	X		X	X	X	X	X
CES-D, QIDS (depression) (47) (48)		X	X		X	X	X	X	
Overall Anxiety Severity Impairment Scale (OASIS) (49)		X	X		X			X	
Perceived Stress Scale (50)		X	X		X			X	
Positive and Negative Syndrome Scale (PANSS-6) (51)		X	X		X	X	X	X	
Clinical COPD questionnaire (CCQ) (52)		X	X		X	X	X	X	
PROMIS Sleep Disturbance Short Form (53)		X	X		X			X	
INTERHEART and WI-PREPARE (55, 56)	X								
Biomeasures									
Weight (57)		X	X		X	X	X	X	
Height		X							
Waist and hip circumference (57)		X						X	
Blood Pressure, Pulse (58, 59)	X	X	X		X	X	X	X	
Exhaled CO	X	X	X		X	X	X	X	X
Pulmonary function test (spirometry) (60)		X	X		X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events (61)		X	X	X	X	X	X	X	X
Biomarkers									
Urine: NNAL, Acrylonitrile (CYMA) Acrolein (3-HPMA) (20, 62, 63)			X			X		X	
Pregnancy test	X		X			X		X	

Procedures during COVID-19:

Remote Visit 1 (Week -3)

Remote Visit 1 will occur over Zoom or the telephone. During Remote Visit 1, participants will be screened using Screener 2. If the participant meets eligibility using Screener 2 the following information will be collected over Zoom or the telephone to determine eligibility in accordance with inclusion/exclusion criteria mentioned above:

1. NIDA Drug Screener
2. Obtain medical and concomitant medication histories
3. Administer all modules in the Mini International Neuropsychiatric Interview (MINI) and current suicide risk assessment (see MINI Standard (version 7.0.2) document). Researchers will administer the MINI mental health diagnostic tool electronically through the nView Health online application. **Procedure for suicide risk at screening:** If a participant scores ≥9 on the MINI suicide module the Psychiatric Medical Monitor (Dr. Ahmad Hameed) will be contacted. The researcher will discuss the score with the Psychiatric Medical Monitor and they will determine if the participant's enrollment into study is appropriate.

If a participant meets the eligibility criteria they will be asked to complete questionnaires via an electronic survey in REDCap. See Revised Table 1 for questionnaires collected at this visit. Biomeasures will not be taken. The study staff will review the study guidelines and provide participants with instructions on how to keep track of the number of their usual brand cigarettes smoked each day for one week by using a cigarette log. All participants will be asked to refrain from using non-study tobacco/nicotine products or other smoked products during the study, but are encouraged to report the use of these products to the study staff. The next study visit will be scheduled for one week later.

Questionnaires for Visit 2 outlined in Revised Table 1 will be sent to the participant via a survey link before the in-person Visit 2. Participants will be encouraged to complete the questionnaires 2 hours before the Visit 2, but will have up to 24 hours to complete them after the visit.

Revised Table 1: Time and events schedule with measures, questionnaires, and biomarkers during COVID-19

Phase	**Baseline**			**Randomized**					**Follow up**
Study Visit Number	**R1**	**2**	**3**	**Phone**	**4**	**5**	**R6**	**7**	**R8**
Study Week Number	**-3**	**-2**	**0**	**1**	**4**	**8**	**12**	**16**	**20**
Measures/Questionnaires									
Study and Non-Study Product Use									
E-cig and Cigarette Use log		X	X	X	X	X	X	X	X
Cigarette liking scales (35)			X		X			X	
E-cig Patterns of Use, E-cig Side Effects, E-cig Evaluation, E-cig Dependence (PSECDI),					X	X	X	X	X
E-cig Perceived Health Risk Rating					X			X	X
E- cig details									X
Basic participant and smoking characteristics									
Demographics (including Social Determinates of Health [SDOH])	X								
Tobacco use history, cigarette details	X								
Medical History	X								
NIDA Drug Use (36)	X							X	
AUDIT-C(37, 38)	X							X	
Environmental tobacco smoke questionnaire (39)		X							
Cigarette Perceived Health Risk		X	X		X			X	
Nicotine dependence (FTND, HONC, PSCDI (31, 40, 41))		X	X		X	X	X	X	X
Nicotine Use Disorder		X						X	
PROMIS Dependence		X						X	
Minnesota Nicotine Withdrawal Scale (42)		X	X		X	X	X	X	X
Questionnaire of Smoking Urges (QSU) (43, 44)		X	X		X	X	X	X	
Confidence to Quit								X	X
Mental Health and Wellbeing									
MINI International Neuropsychiatric Interview (MINI) (34)	X								
Kessler K6 scale (45, 46)		X	X		X	X	X	X	X
CES-D, QIDS (depression) (47) (48)		X	X		X	X	X	X	
Overall Anxiety Severity Impairment Scale (OASIS) (49)		X	X		X			X	
Perceived Stress Scale (50)		X	X		X			X	
Positive and Negative Syndrome Scale (PANSS-6) (51)		X	X		X	X	X	X	
Clinical COPD questionnaire (CCQ) (52)		X	X		X	X	X	X	
PROMIS Sleep Disturbance Short Form (53)		X	X		X			X	
INTERHEART and WI-PREPARE (55, 56)	X								
Biomeasures									

Weight (57)		X	X		X	X		X	
Height		X							
Waist and hip circumference (57)		X						X	
Blood Pressure, Pulse (58, 59)		X	X		X	X		X	
Exhaled CO		X	X		X	X		X	X
Pulmonary function test (spirometry) (60)		X	X		X	X		X	
Concomitant medications	X	X	X	X	X	X		X	X
Adverse events (61)		X	X	X	X	X	X	X	X
Biomarkers									
Urine: NNAL, Acrylonitrile (CYMA) Acrolein (3-HPMA) (20, 62, 63)			X			X		X	
Pregnancy test		X	X			X		X	

Note: R indicates remote visit

Visit 2 (Week -2)

Participants will be asked for their cigarette log from the prior week and to complete questionnaires for Visit 2 outlined in Table 1. Measures will be completed electronically on a participant computer via REDCap or administered by a study coordinator. Participants will be given a laptop with access only to the internet and an individualized REDCap survey will be opened so they can complete direct data entry. Biomeasures will be obtained (e.g., pulmonary function tests, weight, height, waist and hip, exhaled CO, blood pressure, pulse) as outlined in Table 1. Participants will be given SPECTRUM research cigarettes containing a normal amount of nicotine (11.6 mg/cigarette) matching the flavor (regular or menthol) of their usual brand of cigarettes to smoke for the next two weeks. Participants will receive cigarette logs to fill out their cigarettes smoked per day. The number of research cigarettes provided will be 130% of baseline cigarettes per day in order to reduce the chance of running out. This amount may be changed throughout the study according to recent consumption. Participants will be asked to return all opened, unopened and empty cigarette packs to the study center at each visit. All participants will be asked to refrain from using non-study tobacco/nicotine products or other smoked products during the study, but are encouraged to report the use of these products to the study staff. Participants will be compensated for completing the study visit and procedures.

Procedure for suicide risk at all visits where QIDS questionnaire is administered: If participants indicate an answer of > 0 on item 12 of the QIDS questionnaire, the MINI Suicide module will be administered. Scores of ≥ 9 on the MINI Suicide module will require an assessment with a licensed clinician to document a clinical plan and a determination of retention or termination from the study.

Procedures during COVID-19:
Visit 2 will be completed in-person. Participants will be screened for COVID-related symptoms using a modified version of the Patient Screening Questions from the Penn State Health website. The written informed consent process will take place in person using the paper Consent Form HRP-580 uploaded in the “Consent Forms and Recruitment Materials” section of the IRB application. During this process, the usual discussion of procedure, risks, side effects, confidentiality, voluntary participation, and right to refuse participation without prejudice will be explained to the participant. Participants must be capable of understanding the nature of this study, its potential risks, discomforts and benefits before signing consent. Participants will receive a signed copy of the form.

Participants will be asked to provide photo ID to verify the age given in Screener 2. They will have to complete the final eligibility requirements at this visit in accordance with the inclusion/exclusion criteria mentioned above:

1. Obtain urine sample for pregnancy determination for women of child-bearing potential (those who have had a period in the past 12 months) and who have not had a hysterectomy
2. Measure exhaled CO
3. Measure vital signs (blood pressure and heart rate)

Participants will be asked for their cigarette log from the prior week. Additional biomeasures will be obtained (e.g., pulmonary function tests, weight, height) as outlined in Revised Table 1. Participants will be given SPECTRUM research cigarettes containing a normal amount of nicotine (11.6 mg/cigarette) matching the flavor (regular or menthol) of their usual brand of cigarettes to smoke for the next two weeks. Participants will receive cigarette logs to fill out their cigarettes smoked per day. The number of research cigarettes provided will be 130% of baseline cigarettes per day in order to reduce the chance of running out. This amount may be changed throughout the study according to recent consumption. Participants will be asked to return all opened, unopened and empty cigarette packs to the study center at each visit. All participants will be asked to refrain from using non-study tobacco/nicotine products or other smoked products during the study, but are encouraged to report the use of these products to the study staff. Participants will be compensated for completing the study visit and procedures.

Procedure for suicide risk at all visits where QIDS questionnaire is administered: If participants indicate an answer of > 0 on item 12 of the QIDS questionnaire, the MINI Suicide module will be administered. Scores of ≥ 9 on the MINI Suicide module will require an assessment with a licensed clinician to document a clinical plan and a determination of retention or termination from the study.

Visit 3 (Week 0)

Participants will be asked for their cigarette log from the prior week and to complete questionnaires outlined in Table 1. Measures will be completed electronically on a participant computer via REDCap or administered by a study coordinator. Participants will be given a laptop with access only to the internet and an individualized REDCap survey will be opened so they can complete direct data entry. Biomeasures will be obtained (e.g., pulmonary function tests, weight, exhaled CO, blood pressure, pulse) as outlined in Table 1. Urine samples will be collected at this visit. A pregnancy test will be given to women of childbearing potential.

Participants who complete the Baseline Phase and are eligible to continue in the study will enter the Randomized Phase. They will be randomized to either continue to smoke the same NNC SPECTRUM (11.6 mg nicotine) research cigarettes they smoked in the Baseline Phase or switch to VLNC SPECTRUM research cigarettes (0.2 mg nicotine) AND also be randomized to either a nicotine-containing (5% nicotine liquid) or placebo (0% nicotine liquid) JUUL e-cig (JUUL Labs, Inc.). Participants will receive a 4-week supply of research cigarettes (130% of baseline daily consumption) and e-liquid pods to last 28 days until the next appointment. They will be shown how to use the e-cig and how to charge it. Participants may be shown videos from the JUUL website (https://www.juul.com/learn/device) for more information on how to use and charge the device called, 'How to use JUUL' and 'How to set up your JUUL Device'. We will also give them a handout called JUUL E-Cigarette Instructions. Within the JUUL device packaging there is a paper insert with instructions and information. This insert will be given to the participant when we give them the JUUL device. The study staff will give participants e-cig and cigarette use logs and instruct them to record daily use. Participants will be encouraged/provided advice to substitute some of their cigarettes with their e-cigarette.

All participants will be asked about their use of other nicotine/tobacco products and if they vaped/smoked any other substances other than nicotine/tobacco as this could affect the urine biomarkers collected during the study (e.g. carbon monoxide and cotinine levels). Participants will also be reminded to only use research cigarettes and not commercial brand cigarettes, as well as only using the e-liquid pods received by researchers. Participants will be compensated for completing the study visit and procedures.

Between Visits 3 and 4 participants will receive a daily online REDCap survey (named E-cigarette and Cigarette Use Log (Online Survey Version) under Participant Entered Measures) via a text message to their cell phone with a link to the survey using the Twilio services. The survey will ask about the number of e-cig uses, number of cigarettes smoked, and any non-study cigarettes smoked. During the first week of the online survey, participants will also be asked about nicotine withdrawal symptoms. If participants do not have a reliable cell phone and internet access they will complete the information on paper logs.

Procedures during COVID-19:

Visit 3 will be completed in-person. Participants will be screened for COVID-related symptoms using a modified version of the Patient Screening Questions from the Penn State Health website. Questionnaires for Visit 3 outlined in Revised Table 1 will be sent to the participant via a survey link before the in-person visit. Participants will be encouraged to complete the questionnaires 2 hours before the visit, but will have up to 24 hours to complete them after the visit. Participants will be asked for their cigarette log from the prior week. Biomeasures will be obtained (e.g., pulmonary function tests, weight, exhaled CO, blood pressure, pulse) as outlined in Revised Table 1. Urine samples will be collected at this visit. A pregnancy test will be given to women of childbearing potential.

Participants who complete the Baseline Phase and are eligible to continue in the study will enter the Randomized Phase. They will be randomized to either continue to smoke the same NNC SPECTRUM (11.6 mg nicotine) research cigarettes they smoked in the Baseline Phase or switch to VLNC SPECTRUM research cigarettes (0.2 mg nicotine) AND also be randomized to either a nicotine-containing (5% nicotine liquid) or placebo (0% nicotine liquid) JUUL e-cig (JUUL Labs, Inc.). Participants will receive a 4-week supply of research cigarettes (130% of baseline daily consumption) and e-liquid pods to last 28 days until the next appointment. They will be shown how to use the e-cig and how to charge it. Participants may be shown videos from the JUUL website (https://www.juul.com/learn/device) for more information on how to use and charge the device called, 'How to use JUUL' and 'How to set up your JUUL Device'. We will also give them a handout called JUUL E-Cigarette Instructions. Within the JUUL device packaging there is a paper insert with instructions and information. This insert will be given to the participant when we give them the JUUL device. The study staff will give participants e-cig and cigarette use logs and instruct them to record daily use. Participants will be encouraged/provided advice to substitute some of their cigarettes with their e-cigarette.
All participants will be asked about their use of other nicotine/tobacco products and if they vaped/smoked any other substances other than nicotine/tobacco as this could affect the urine biomarkers collected during the study (e.g. carbon monoxide and cotinine levels). Participants will also be reminded to only use research cigarettes and not commercial brand cigarettes, as well as only using the e-liquid pods received by researchers. Participants will be compensated for completing the study visit and procedures.

Between Visits 3 and 4, participants will receive a daily online REDCap survey (named E-cigarette and Cigarette Use Log (Online Survey Version) under Participant Entered Measures) via a text message to their cell phone with a link to the survey using the Twilio services. The survey will

ask about the number of e-cig uses, number of cigarettes smoked, and any non-study cigarettes smoked. During the first week of the online survey, participants will also be asked about nicotine withdrawal symptoms. If participants do not have a reliable cell phone and internet access they will complete the information on paper logs.

Phone Call (Week 1)

Study staff will call participants to check in on their use of the study cigarettes/e-cig, remind them to use the study products, document any adverse events, and remind them to fill out their e-cigarette and cigarette use log on paper and through the online surveys. If any data on the e-cigarette and cigarette use log online survey is missing it will be collected over the phone with the participant.

Visit 4-7 (Weeks 4, 8, 12, 16)

Participants will return their e-cig and cigarette use log, and have a comprehensive set of measures recorded according to the visit (Table 1). Measures will be completed electronically on a participant computer via REDCap or administered by a study coordinator. Participants will be given a laptop with access only to the internet and an individualized REDCap survey will be opened so they can complete direct data entry. Women of child bearing potential will be retested for pregnancy at Visits 5 and 7.

The study staff will give participants e-cig and cigarette use logs and instruct them to record daily use at each visit. All participants will be asked about their use of other nicotine/tobacco products and if they vaped/smoked any other substances other than nicotine/tobacco at each visit as this could affect the urine biomarkers collected during the study (e.g. carbon monoxide and cotinine levels). Participants will be encouraged/provided advice to substitute some of their cigarettes with their e-cigarette.

Participants will receive a 4-week supply of research cigarettes (130% of daily consumption) and e-liquid pods to last approximately 28 days until the next appointment. Participants will be asked to return all opened, unopened and empty cigarette packs and all used/unused e-liquid pods to the study center at each visit in order to monitor use.

At Visit 7, participants will return all used and unused research cigarette packs. No more cigarettes will be given. Participants will be allowed to keep their e-cig and unused e-liquid pods until the next visit. Participants will return their e-cig and cigarette use logs. Urine samples for biomarkers will be taken. Participants will complete all biomeasures and questionnaires outlined in Table 1. Participants will be advised to quit smoking completely and provided with the quitline number and sources of free/low cost nicotine replacement therapy (NRT) (see Cigarette Smoking Cessation Tools handout document). The Surgeon General booklet will also be give (see the Consumer Surgeon General Report Booklet document). Participants will be asked about their plans to either (a) go back to their own cigarettes only (b) go back to own cigarettes but supplement with an e-cig, (c) continue using an e-cig only, or (d) quit tobacco/e-cigs completely. Participants will be compensated for completing the study visit and procedures.

A study pulmonologist was added to the study team. We will be monitoring lung function using pulmonary function testing that will be completed at Visits 4-7. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event. These adverse events will be reviewed by the Safety Monitors in a timely manner. In cases where the Safety Monitor suspects that a participant may be having a respiratory adverse event related to

the study product, a study pulmonologist 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. For more urgent and/or serious adverse events, the Safety Monitor and/or the study pulmonologist will be consulted and immediate medical attention will be sought if needed.

Procedures during COVID-19:

Visits 3-5 and 7 will be completed in-person. Participants will be screened for COVID-related symptoms using a modified version of the Patient Screening Questions from the Penn State Health website. Remote Visit 6 will be completed remotely over Zoom or the telephone. Questionnaires for visits outlined in Revised Table 1 will be sent to the participant via a survey link before the in-person visit. Participants will be encouraged to complete the questionnaires 2 hours before the visit, but will have up to 24 hours to complete them after the visit. Participants will return their e-cig and cigarette use log. Biomeasures will be taken as outlined in Revised Table 1. No biomeasures will be collected at Remote Visit 6. Women of child bearing potential will be retested for pregnancy at Visits 5 and 7.

The study staff will give participants e-cig and cigarette use logs and instruct them to record daily use at each visit. All participants will be asked about their use of other nicotine/tobacco products and if they vaped/smoked any other substances other than nicotine/tobacco at each visit as this could affect the urine biomarkers collected during the study (e.g. carbon monoxide and cotinine levels). Participants will be encouraged/provided advice to substitute some of their cigarettes with their e-cigarette.

Participants will receive a 4-week supply of research cigarettes (130% of daily consumption) and e-liquid pods to last approximately 28 days until the next appointment. At Visit 5, participants will receive an 8-week supply of e-cigarettes and cigarettes due to Remote Visit 6 being a remote visit. Participants will be asked to return all opened, unopened and empty cigarette packs and all used/unused e-liquid pods to the study center at each visit in order to monitor use.

At Visit 7, participants will return all used and unused research cigarette packs. No more cigarettes will be given. Participants will be allowed to keep their e-cig and unused e-liquid pods until the next visit. Participants will return their e-cig and cigarette use logs. Urine samples for biomarkers will be taken. Participants will complete all biomeasures and questionnaires outlined in Revised Table 1. Participants will be advised to quit smoking completely and provided with the quitline number and sources of free/low cost nicotine replacement therapy (NRT) (see Cigarette Smoking Cessation Tools handout document). The Surgeon General booklet will also be given (see the Consumer Surgeon General Report Booklet document). Participants will be asked about their plans to either (a) go back to their own cigarettes only (b) go back to own cigarettes but supplement with an e-cig, (c) continue using an e-cig only, or (d) quit tobacco/e-cigs completely. Participants will be compensated for completing the study visit and procedures.

A study pulmonologist was added to the study team. We will be monitoring lung function using pulmonary function testing that will be completed at Visits 4, 5, 7. Any significant worsening (10% worsening or greater) in pulmonary function will be documented as an adverse event. These adverse events will be reviewed by the Safety Monitors in a timely manner. In cases where the Safety Monitor suspects that a participant may be having a respiratory adverse event related to the study product, a study pulmonologist 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. For more urgent and/or serious adverse events, the Safety Monitor and/or the study pulmonologist will be consulted and immediate medical attention will be sought if needed.

Follow-up Visit 8 (Week 20)

All participants will be followed up at a visit 4 weeks after their last visit of the Randomized Phase in order to find out their cigarette/e-cig consumption and any attempts in abstinence after participating in the randomized portion of the trial. Participants will return any final e-cigs and e-liquid pods to the study team by either dropping them off to the researcher or scheduling a pick up time with the researcher. If neither of these options can be arranged the participants will be advised how to properly dispose the products themselves. Participants will complete an exhaled CO measurement plus all measures listed in Table 1. Participants will be compensated for completing the study visit procedures.

Procedures during COVID-19:

Remote Visit 8 will be completed remotely over Zoom or the telephone. All participants will be followed up 4 weeks after their last visit of the Randomized Phase in order to find out their cigarette/e-cig consumption and any attempts in abstinence after participating in the randomized portion of the trial. Questionnaires for visits outlined in Revised Table 1 will be sent to the participant via a survey link before the in-person visit. Participants will be encouraged to complete the questionnaires 2 hours before the visit, but will have up to 24 hours to complete them after the visit. Participants will return their e-cig and any e-liquid pods in a pre-paid envelope addressed to the study site. In cases where participants report being abstinent from cigarettes in the past 7 days at Visit 8, we will verify with a carbon monoxide reading (which bio-chemically validates abstinence). We will plan to send individual CO monitors for participants that can be mailed to the participant's house. Participants will use the personal devices to complete a CO measurement while on ZOOM with the researcher. Participants will be compensated for completing the study visit procedures.

Unscheduled Visits

If a participant requires additional study product (e.g., cigarette packs, e-cig pods), or if the e-cig fails, they may call the research center to schedule a time to obtain additional products (in-person).

Appointment Reminders

Phone call, text, and email reminders will be used throughout the study to remind participants of their next visits (approximately 1-2 days prior). Also, visit time/date confirmation and study center directions will be emailed/mailed to the participant prior to Visit 1 (see First Appointment Reminder document). 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.

Biospecimen Processing

All urine samples collected will be stored and analyzed in the project biomarkers core lab led by Dr. John Richie.

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.

Missed Visit Procedures

Participants will be called at least once to reschedule a missed Visit 1. For participants who do not show up for any other in-person visit, up to 3 phone/email attempts will be made to contact them to reschedule their appointment.

7.3 Duration of Participation

The participants who complete all study contacts will participate for a total of 23 weeks.

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

7.4.1 Description

Research cigarettes (SPECTRUM) used in the study are provided by the NIDA Drug Supply Program (Notice Number NOT-DA-14-004). They are available from the Research Triangle Institute (RTI, North Carolina) with the same additives as commercial cigarettes but contain varying levels of nicotine. The cigarettes come in either menthol or non-menthol cartons. Each carton includes 10 packs of cigarettes with 20 cigarettes per pack. The physical characteristics, chemical profiles and pharmacokinetics of the research cigarettes have been well characterized (66-68).

We will use JUUL e-cigs purchased from JUUL Labs, Inc. The JUUL e-cig is a closed-system device that contains 2 main components- a disposable pod that contains liquid and a heating coil, and a USB-rechargeable battery. The disposable pods contain 0.7 mL of e-cig liquid and contain either 0% or 5% nicotine strength by weight. The device is rechargeable with a USB charging dock. The JUUL e-cig device meets battery and electrical testing standards. The safety features of JUUL include breath activation to prevent the device from turning on accidentally and a low power setting that limits its peak temperature.

We had originally proposed to use the NIDA Standardized Electronic Cigarette (SREC) because (a) it is available with a placebo matching the nicotine variety (b) it has known nicotine pharmacokinetics (mean Cmax = 17.7 ng/ml after 10 puffs in 4.5 minutes) and (c) it is known to deliver low concentrations of toxicants relative to both cigarettes and some other e-cigs(69, 70). In a laboratory study of chemicals emitted by SREC here at Penn State, we concluded that "*Overall, SREC was more efficient at aerosol and nicotine production than both Blu and Vuse. In terms of carbonyl and free radical levels, SREC delivered lower or similar levels to both other devices.*"(69) However, the e-cig company manufacturing the NIDA SREC product has experienced technical difficulties as it moved from producing small numbers of this e-cig to manufacturing a large number of e-cigs for numerous clinical trials. We cannot use this product until these problems have been resolved. Our NIH program officer agreed with us that in this ongoing situation, for this protocol (which is not required to use the SREC device), it makes sense to use JUUL.

The reasons for selecting JUUL are the same as reasons we originally selected the SREC, (a) it is available with a placebo matching the nicotine variety (b) it has known nicotine pharmacokinetics (baseline-adjusted mean Cmax = 15.4 ng/ml after 10 puffs in 4.5 minutes, as compared with 20.1 ng/ml from a Pall Mall cigarette(71)) and (c) it is known to deliver low

concentrations of toxicants relative to both cigarettes and some other e-cigs (72). Our own lab here at Penn State studied JUUL in a similar manner to SREC and concluded that "*These findings suggest that oxidative stress and/or damage resulting from JUUL use may be lower than that from cigarettes or other e-cig devices*." Other labs, independent of JUUL, have studied the JUUL product and come to very similar conclusions: "*JUUL's nicotine-normalized formaldehyde and total aldehyde yields are lower than other previously studied ECIGs and combustible cigarettes.*"(73). One of the key advantages of JUUL is that it has a built-in temperature-controlled circuit that prevents the temperature of the liquid from exceeding 215°C. In other e-cigs overheating of the coil as the liquid in the wick runs low is one factor suspected of causing higher toxicant emissions (but still far lower than cigarettes). JUUL's design avoids this. Finally, in September 2019, FDA announced a new deadline for all e-cigarette manufacturers to apply for the right to continue to stay on the market (September 9, 2020). These Pre-market Tobacco Product applications (PMTAs) require all manufacturers to provide FDA with a very comprehensive set of information about their product, including marketing plans. It is likely that only the major e-cig manufacturers will be capable of submitting acceptable PMTAs to legally stay on the market after September 9, 2020. While it is impossible to know the outcome of that process, we need to select a product to use in our trial that appears likely to remain on the market in the foreseeable future, and so that is another reason for selecting JUUL.

7.4.2 Treatment Regimen

At Visit 2, all participants will be given Normal Nicotine Cigarettes (11.6 mg nicotine/cigarette) to use for 2 weeks. At Visit 3, participants will be randomized into one of the 4 arms described below:

	5% Nicotine E-cig	**0% Nicotine E-cig**
Normal Nicotine Cigarettes (NNCs) (11.6 mg nicotine/cigarette)	Arm 1	Arm 2
Very Low Nicotine Cigarettes (VLNCs) (0.2 mg nicotine/cigarette)	Arm 3	Arm 4

Participants will be provided with these products starting at Visit 3 (Week 0) and continue to use these products ad libitum through Visit 7 (Week 16).

7.4.3 Method for Assigning Subject to Treatment Groups

Eligible participants will be allocated to one of the four conditions using a blocked randomization with a 1:1:1:1 ratio of condition assignments via REDCap. The randomization table will be created by the study statistician and only unblinded staff will have access to it.

7.4.4 Subject Compliance Monitoring

Compliance will be monitored throughout the trial by a) daily product use logs; b) product accountability logs where the amount of product dispensed will be recorded and unused products collected and recorded; and c) questionnaires administered during study contacts regarding the use of other tobacco or nicotine products. Any problems that arise or are anticipated will be discussed and problem-solved with the coordinator. Furthermore, exhaled CO measurements will be collected throughout the study to verify smoking intensity and exposure levels.

7.4.5 Blinding of the Test Article

Research cigarettes: An unblinded staff member will receive and remove all identifiers from cigarette cartons and replace them with our own blind code labels. The blind code labels will be unique to each carton and correspond to a nicotine dose level. There are no identifiers on individual packs of cigarettes. The blinded researcher will not be involved in the packing and labelling of the research cigarettes.

E-cigs: The e-cig products will be received by unblinded staff who will appropriately package the pods and e-cig parts (device+charger) into packs/kits for the participants. The kits will have assigned numbers corresponding to a nicotine dose level, and the participants will be randomly assigned to a kit number at the randomization visit. The blinded researcher will not be involved in the packing and labelling of the kits.

All other study personnel, including lab staff, will remain blinded until the last randomized participant completes Visit 8.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Research cigarettes: Experimental cigarettes will be provided free of charge to the investigators via the NIDA Drug Supply Program (Notice Number NOT-DA-14-004). They will be shipped in boxes to Penn State from the Research Triangle Institute. The boxes will contain cartons of cigarettes- 10 packs in each carton with 20 cigarettes in each pack. Each carton is packaged by nicotine content and menthol (green)/non-menthol (blue) flavoring.

E-cigs: The JUUL device will be purchased from JUUL Labs, Inc. in its standard packaging and shipped to Penn State and will be received by unblinded staff. Pre-filled, sealed, disposable pods containing 0.7 mL of e-cig liquid will also be purchased from JUUL Labs, Inc. The research team will maintain the certificates of analysis or lot information for the JUUL products used in the study.

7.4.6.2 Storage

Research cigarettes: Cigarettes will be stored in standard freezers at Penn State in a locked space that is only accessible by unblinded research staff involved in our studies. A service provided by Penn State will monitor and record the temperature of the freezers.

E-cigs: Devices and e-liquids will be stored at room temperature at Penn State in a locked space that is only accessible by unblinded research staff involved in our studies. A service provided by Penn State will monitor and record the temperature/humidity of the room.

7.4.6.3 Preparation and Dispensing

All receiving, sorting, blinding of the study products will be done in secure, locked space for unblinded research staff at Penn State Hershey.

Research cigarettes: Once the cigarettes are received, they will be blinded by the unblinded study staff with unique blind codes. At Visit 3, following

confirmation of eligibility for randomization, staff will use blind codes to dispense the cartons to participants. Staff will prepare a bag of cigarette packs that will be given to the study coordinator for the participant. The blinded researchers will not be involved in the packing and labeling of the cigarettes.

E-cigs: The pods will come pre-filled in sealed packages. They will be prepared for participants by unblinded staff and stored with unique identifiers. Unblinded staff will appropriately package kits containing two JUUL devices and a supply of pods for the participants. At Visit 3, 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.

7.4.6.4 Return or Destruction of the Test Article

Research cigarettes: Participants will be instructed to return all research cigarette packs at the next in-person visit, regardless of whether they are empty, unopened or partially used. Any unused research cigarettes that are returned from the participant at the end of the study will be destroyed on site according to the general policy for drug disposal by the Investigational Drug Pharmacy.

E-cigs: Participants will be instructed to return all used and unused e-liquid pods to the study at each in-person visit to monitor use. We will ask participants to return the e-cig to the study site at the last in person visit and we will dispose of it on-site. Any unused pods that are returned at the last in person visit will be destroyed on site according to the general policy for drug disposal by the Investigational Drug Pharmacy.

Procedures during COVID-19:
Participants will receive a pre-paid envelope at Visit 7 to return all of their unused pods and e-cig to the study site. Any unused pods and e-cigs will be destroyed on site according to the general policy for drug disposal by the Investigational Drug Pharmacy.

7.4.6.5 Prior and Concomitant Therapy

Concomitant medications will be collected at baseline and regularly throughout the trial 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 other medications that will interfere with the participant's ability to participate.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We plan to enroll 300 participants in order to randomize 240 participants (60 in each of the four study arms).

8.2 Sample size determination

For the sample size calculation, we have used data for completers of our recent randomized controlled trial(8) to estimate magnitude of effects for the primary endpoint (NNAL, pmol/mg creatinine). Additionally, we have used data from Donny et al.'s trial [Table Supplement 15] (5). Based on their paper, the difference in log NNAL between the 0.4 mg/g group (sample size 96) and the 15.8 mg/g group (sample size 100) is log(0.78)= -0.248 with a confidence interval of log(c(0.64, 0.96)) = (-0.446, -0.0408). Based on this, the within group standard deviation of log NNAL is 0.562. Combining the above two datasets, we shall assume that the effect size is 58% of the size of the standard deviation in the sample size calculation, slightly larger than reported above because our trial will have 16 weeks of follow-up. Let arm 3 of the trial be the group to which arms 1, 2 and 4 will each be compared. To adjust for multiple comparisons, the type one error level alpha is taken to be .05/3=0.017. The sample size of 60 subjects in each of the 4 arms is needed to provide 80% power of detecting a difference between any three arms and arm 3. In addition this trial will have over 95% power, at a 5% type 1 error rate, to detect the same effect on abstinence found in our recent RCT of VLNCs one month after the end of the randomized phase (20.2% in those randomized to VLNCs vs. 6.4% in those randomized to NNCs).

8.3 Statistical methods

Basic baseline statistics including means (standard deviations) and frequency distributions (percentages) will be reported for demographic characteristics, smoking characteristics, nicotine dependence, and nicotine and toxicant exposure. Characteristics will be reported by the four treatment arms to identify treatment arm imbalances. Numerical baseline characteristics will be compared among four arms using ANOVA tests or nonparametric Kruskal-Wallis tests when appropriate. Categorical variables will be compared using chi-square tests or Fisher's exact tests. The focus of the statistical analysis will be the difference between four trial arms in terms of the biomarkers of toxicity and health effects. Analyses will be conducted in two approaches, which will address our research questions in two different angles. The first approach is a simplified and streamlined one, the longitudinal measurements of these biomarkers over the 16-week period will be summarized by using just the baseline (visit 3, pre-randomization) and final (visit 7, end of randomization period) measurements. Analysis of Covariance (ANCOVA) models will be used to compare the final measurements among the four arms, while the baseline measurements will be treated as controlled covariates in the modelSpecifically, the comparisons between arms 1 and 3 and between arms 2 and 4 answer whether switching to very low nicotine cigarettes leads to lower markers of harm as compared to continuing on normal nicotine cigarettes. This addresses specific Aim 1. Furthermore, we will study if this reduction is the same when combined with 5% nicotine e-cigs (arms 1 and 3) and combined with placebo e-cigs (arms 2 and 4). Similarly, comparison between arm 1 and arm 2 reveals if access to nicotine versus placebo e-cigs impacts these biomarkers. This will address Aim 2. In particular, we will test if the arm 3 has the best outcome as stipulated in Aim 2. These analyses will be conducted using ANCOVA models with interaction terms between traditional cigarettes (normal nicotine vs. very low nicotine) and e-cig (5% vs. 0%). Appropriate transformation may be done on some of the outcome variables (for example log-transformation) to make sure the underlying statistical assumptions are all satisfied. Note that for NNAL, one of our main biomarkers of toxicity; it can only be analyzed using the first approach due to the limitation of number of measures.

The second approach for biomarker analysis will use the longitudinal data analysis to model all the repeated measurements of these biomarkers over the entire 16 weeks. Their trajectories will be plotted for each of the 4 arms. Linear mixed-effect models will be used to model the biomarker measurements on the following predictors: time after randomization (X1, which can be measured in weeks (continuous or visit number (categorical)), normal vs. low nicotine cigarettes (X2), 5% nicotine e-cig vs. placebo e-cig (X3), the interaction between cigarette and e-cig (X2*X3), and the interaction between X1 and X2, X3, X2*X3. In particular, the three-way interaction of X1, X2 and X3 indicates an interaction between cigarette type (NNC versus VLNC) and e-cig type (nicotine versus placebo) on their effect on the change of these markers of harms to health over time. Note that the time variable (X1) can be treated as either categorical or continuous, which will lead to different statistical models – growth curve model vs repeated-measure ANOVA models. If X1 is treated as categorical, then the estimated means and 95% confidence interval (CI) values of the outcome variables will be reported using tables. If X1 is treated as continuous, then the point estimates and 95% CI of the coefficients (rate of changes) will be reported. The baseline (before randomization) measures of the outcome variables will be included in the model as a controlled covariate. Family-wise type-I error rate due to multiple comparisons will controlled at the visit level (if X1 is treated as categorical) using Bonferroni method. Again, appropriate transformation of the outcome variable may be carried out – similar to the first approach.

Intent-to-treat (ITT) principle will be adopted for the analyses in both approaches. Additionally, the measurements of tobacco use and addiction and measurements of mental health will be monitored and summarized, and will be compared across these arms in a similar statistical fashion as described above. Self-reported compliance will be reported for all participants. For participants in arm 4 (VLNC plus placebo ecigs) their compliances will be further evaluated using biomarkers. Comparison on the outcome variables will be made between compliers vs non-compliers within arm 4 participants only. All analyses will be conducted using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA) and R Programming language version 3.6.1 or higher (R Foundations). All tests will be two-sided and the statistical significance level to be used is 0.05.

Adjusted models will evaluate the treatment effect while adjusting for covariates, such as gender, age, race, SDOH scoring, and other baseline factors.

9.0 Data and Safety Monitoring Plan

9.1 Periodic evaluation of data

The PI and research staff will be responsible for the daily oversight of subject safety. Subjects will be seen by research staff while in the study that will assess adverse events and take appropriate medical actions if necessary. The Safety Monitor will review AEs on a weekly basis and study staff will discuss subject's experiences during meetings when necessary. The Safety Monitor will consult with the study pulmonologist (Dr. Rebecca Bascom) on respiratory related adverse events. In addition, the study 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.

9.2 Data that are reviewed

The Data and Safety Monitoring Report will include:

- Accrual and retention
- Baseline sociodemographic characteristics
- Adverse events and serious adverse events
- Protocol deviations/violations
- Participants' ability to achieve study requirements

- Significant changes in mental health status including suicidal ideation
- Changes in psychological measures of anxiety and depression (OASIS and QIDS)
- Changes in cigarette consumption from baseline
- Exhaled carbon monoxide increase from baseline
- Changes in lung function via pulmonary lung function tests
- Changes in lung function via the Clinical COPD questionnaire

9.3 Method of collection of safety information

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

9.4 Frequency of data collection

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

9.5 Individuals reviewing the data

A committee will be established to review the data that will include:

1. Julio Fernandez-Mendoza, Ph.D., Department of Psychiatry and Behavioral Health, Penn State College of Medicine*
2. Erika Saunders, M.D., Department of Psychiatry and Behavioral Health, Penn State College of Medicine
3. David Rabago, M.D., Department of Family and Community, Penn State College of Medicine

*DSM Committee Chair

The committee will review the report and make appropriate recommendations to continue research as is, continue research with modification, or discontinue research in the event of significant efficacy issues or unacceptable adverse events. A copy of the committee's review of the Data and Safety Monitoring Report will be shared with Penn State IRB and any other appropriate regulatory bodies.

9.6 Frequency of review of cumulative data

A Data and Safety Monitoring Report with cumulative data will be generated every 6 months after recruitment begins.

9.7 Statistical tests

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

9.8 Suspension of research

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

10.0 Risks

Switching cigarette brands: Before being randomized in the study you will switch from your usual brand of cigarettes to study cigarettes that are similar in nicotine to your own brand of cigarettes to smoke for 2 weeks. The cigarettes you are given throughout this study may have different characteristics (i.e. nicotine level, ventilation, length, etc.) than your usual brand. So you could experience symptoms related to different strength or sensory effects from the study cigarettes, such as harshness in your throat or chest.

Increased compensatory smoking: Participants may be given cigarettes that have very low levels of nicotine in them which may lead to compensatory smoking and in turn increased levels of toxicant exposure. In prior studies, compensatory smoking was minimal and higher levels of toxicant exposure were generally not observed. Cigarette consumption and exhaled carbon monoxide will be monitored throughout the trial.

E-cig use: There may be some unknown risks related to the use of e-cigs. 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, sore throat, mouth ulcers, dizziness, headache, nausea, and hiccups.

- 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 (or rash).
- There are reports that some people who use e-cigarettes have experienced seizures, with most involving youth or young adult users. Participants with a history of seizures or take medications to prevent seizures will be excluded from the study.
- There have been some reports of serious lung illnesses among those who used e-cigarettes, and even some cases of death as a result. The cause of all deaths has not been identified. The investigations being conducted by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have found that the majority of people experiencing these illnesses were using 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.

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.

Nicotine withdrawal symptoms: Ceasing nicotine may result in nicotine withdrawal symptoms (e.g., irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, insomnia/sleep problems, impatience, headache, difficulty concentrating). It is possible that nicotine withdrawal symptoms could affect a pre-existing mental health condition. These symptoms will be monitored at each visit.

New pregnancy or intention 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.

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.

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.

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).

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, participants will be provided with a list of phone numbers for organizations that can provide information and referrals should they need them.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

There is no guaranteed direct benefit to the individuals who participate in this study. However, those who participate and switch completely 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.

11.2 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 while also providing information on the effects of using e-cigs and smoking reduction strategies.

12.0 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, pulmonary function test), a participant is found to have a result outside of clinical norms, the result will be discussed with the participant at the visit where the result is identified. This information will be written in the Critical Value Letter so that it can be shared with the participant and/or their doctor. 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. Overall study results will not be shared with participants.

A Participant Randomization email will be sent to all participants who were randomized in the study. The email will state their randomization assignments for both the study cigarettes and e-cigarette/pods. They will be told if study cigarettes either contained normal nicotine or very low nicotine and if the e-cigarette pods either contained nicotine or zero nicotine.

13.0 Subject Payment and/or Travel Reimbursements

Compensation for study participation is outlined in the Payment Table below. The total possible payment is $550. Payments will be issued on the Greenphire ClinCard.

Payment Table

Study Visit #	Visit Completion	Transportation (in-person visits)	Incentive	Total
1	$0			
2	$60	$20		$80
3	$60	$20		$80
4	$60	$20		$80
5	$60	$20		$80
6	$60			$60
7	$60	$20		$80
8	$60		$30	$90
			Total possible:	$550

14.0 Economic Burden to Subjects

14.1 Costs

There are no costs that subjects will be responsible for related to the research.

14.2 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.

15.0 Resources Available

15.1 Facilities and locations

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

Procedures during COVID-19:
All in-person visits will take place in the Penn State Hershey Clinical Research Center. Remote visits will take place over the telephone or Penn State Health Zoom.

15.2 Feasibility of recruiting the required number of subjects

Generally, those with mental health conditions have a higher smoking prevalence than the general population (32% with mental illness, 23.3% without mental illness). Additionally, the estimated smoking prevalence in 2017 in Pennsylvania was 19%.

We had success in recruiting and screening for our recently completed trial on SMHC(8), where participants were required to meet diagnostic criteria for a mood or anxiety disorder on the MINI International Neuropsychiatric Interview (MINI).(34) For this planned trial we have chosen to include those with these plus additional mental health conditions so the sample is more broadly representative of the wider group of potentially vulnerable smokers.

15.3 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 20% time for this study.

15.4 Availability of medical or psychological resources

All of our participants will be seen by appropriately trained research staff and research nurses in the Clinical Research Center while in the study. We have established a protocol for assessing suicide risk that requires the availability of a licensed psychiatrist to evaluate participants if they indicate any score on the MINI suicide ≥ 9 at screening or follow-up. Any score on the QIDS questionnaire > 0 will trigger the study staff to complete the MINI Suicide module. Scores ≥ 9 on the MINI will trigger a psychiatric assessment. Any urgent health problem will require accompanying the participant to the ER, which is located in the same building.

Procedures during COVID-19:
If a psychiatric assessment is triggered during a remote visit, the study psychiatrist will contact the participant over the phone or Zoom.

15.5 Process for informing Study Team

All members of the study team will have completed all necessary training and documentation will be collected. The project will also have a shared workspace to upload project specific documentation, for example, training documents, SOPs, IRB documents, and current protocols. Regular team meetings will be conducted where study procedures, questions, and issues will be discussed and resolved.

16.0 Other Approvals

16.1 Other Approvals from External Entities

The FDA will require submission and approval of an Investigational Tobacco Product (ITP) application for use of the study products.

16.2 Internal PSU Committee Approvals

Check all that apply:

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

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

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

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

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

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

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

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

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

17.0 Multi-Site Study

N/A

17.1 Other sites

N/A

17.2 Communication Plans

N/A

17.3 Data Submission and Security Plan

N/A

17.4 Subject Enrollment

N/A

17.5 Reporting of Adverse Events and New Information

N/A

17.6 Audit and Monitoring Plans

N/A

18.0 Adverse Event Reporting

18.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug

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

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

18.2 Recording of Adverse Events

Research subjects will be routinely questioned about adverse events at in-person study visits. Adverse event data will be directly coded into REDCap.

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

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

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

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

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.

18.3 Causality and Severity Assessments

The Safety Monitors will promptly 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 Safety Monitor will be available for consultation by phone or immediate medical attention will be sought (i.e. Emergency room). The Safety 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 Safety 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.

18.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

18.4.1 Written IND/IDE Safety Reports

N/A

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

N/A

18.5 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.

18.6 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/cigarette product allocation.

18.7 Stopping Rules

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

19.0 Study Monitoring, Auditing and Inspecting

19.1 Study Monitoring Plan

19.1.1 Quality Assurance and Quality Control

The overall responsibility for data quality and study conduct lies with the PI. 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 locked in the research offices of the PI. Any additional data that is generated (i.e., electronic PFT), 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.

Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. Data that will be entered by participants directly will be reviewed for completeness. Out of range values will be identified immediately when the participants are completing online data forms to reduce keying errors.

19.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate.

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

The **Safety Monitors** (Dr. Ahmad Hameed and Dr. Christopher Sciamanna) are licensed medical professionals who will make the final assessments and causality of AEs. They will be available to answer any questions concerning AEs. In cases where the Safety Monitor suspects that a participant may be having a respiratory adverse event related to the study, the study pulmonologist will be consulted.

20.0 Future Undetermined Research: Data and Specimen Banking

20.1 Data and/or specimens being stored

Specimens (urine) collected during the study will be banked for future undetermined research. Specimens will be stored with a participant ID code attached along with the visit number and date. All other identifiable data associated with the ID code will be retained in REDCap.
Questionnaire data collected during the study that is used for future undetermined research will be de-identified.

20.2 Location of storage

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

20.3 Duration of storage

Questionnaire data and specimens will be stored indefinitely.

20.4 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 as minimally necessary.

20.5 Procedures to release data or specimens

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

20.6 Process for returning results

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

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22.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form