PENNSTATE

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

Protocol Title:

Switching to Progressively Reduced Nicotine Content Cigarettes in Smokers with Lower Socioeconomic Status

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- All guidance language appears in ***red italics*** and should be deleted from the final version of the protocol.

Table of Contents

1. Objectives

1.1. Study Objectives

Specific Aims

1. Determine the effect of progressive nicotine content reduction on nicotine and its metabolites and other biomarkers of smoking exposure.
    a. Determine the effects of RNC (reduced nicotine content) cigarettes in both black and white smokers of lower SES (socioeconomic status) over an 18 week trial period. Subjects will be randomized to either, (i) gradual reduction in reduced nicotine content cigarettes, or (ii) cigarettes containing the nicotine content of their usual brand. It is expected that the gradual reduction of nicotine from progressively lowering nicotine exposure will lead to lower levels of blood nicotine metabolites and nicotine-derived 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol)(NNAL), while not affecting cigarettes smoked per.
    b. Determine the modifying effect of menthol on progressive nicotine content reduction and biomarkers. It is expected that menthol will not modify the effect of progressive RNC cigarettes on the above biomarkers.
2. Determine the predictors of participant drop-out/relapse. We hypothesize that compensatory smoking behavior as measured by smoking topography and expired carbon monoxide (CO), a higher baseline nicotine dependence behavioral score, will be associated with dropout/ relapse.
3. Determine if a gradual reduction in RNC cigarettes vs. same nicotine content is associated with a reduction in stress. Psychological stress and nicotine stimulate the production of cortisol, a biomarker of stress pathways. It is expected that nicotine reduction will lead to initially higher levels

of psychological stress and cortisol associated with withdrawal but lowered levels of psychological stress/cortisol with long-term nicotine reduction.

1.2. Primary Study Endpoints

1.2.1. Product compliance/drop-out

1.3. Secondary Study Endpoints

1.3.1. Nicotine and withdrawal symptoms- Fagerstrom Test for Nicotine Dependence, Hooked on Nicotine Checklist, Stages of Change, Minnesota Withdrawal Scale, Questionnaire on Smoking urges

1.3.2. Nicotine metabolites, smoke exposure biomarkers, oxidative stress biomarkers

1.3.3. Smoking topography (puff volume, puff count, puff duration, puff intensity)

1.3.4. Stress biomarkers (cortisol) and questionnaires (Kessler 6, Perceived stress, CESD)

2. Background

2.1. Scientific Background and Gaps

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) [1] gave the Food and Drug Administration (FDA) jurisdiction over the regulation of all tobacco products including their nicotine content. It gives the FDA authority under Section 907 of the Federal Food, Drug, and Cosmetic Act (FDCA) to require standards for tar and nicotine levels to protect public health. It also bans cigarettes with flavoring additives except menthol. Under this act, a major strategy to reduce harm from tobacco is lowering the nicotine content and delivery down to levels at which they are no longer addictive. The effectiveness of this strategy needs to be demonstrated in different populations whose response to RNC cigarettes might be substantially mediated by personal or environmental factors. For example, blacks have a lower quit rate than whites, and low SES continues to be a major predictor of smoking. Low SES smokers may be particularly susceptible to smoking because they live in more distressed conditions. Low SES smokers are less likely to quit and are more highly dependent.

2.2. Previous Data

A randomized, parallel arm, semi-blinded study examined the effects of reduced nicotine cigarettes on smoking behavior, toxicant exposure, dependence and abstinence. Participants were assigned to one of three groups over a six week intervention period: 1) 0.05 mg nicotine yield cigarettes (Quest 3); 2) 0.3 mg nicotine yield cigarettes (Quest 2); or 3) 4 mg nicotine lozenge. Compensatory smoking behavior, biomarkers of exposure, tobacco dependence, and tobacco withdrawal and abstinence rate were assessed. Unlike the 0.3 mg cigarettes, 0.05 mg cigarettes were not associated with compensatory smoking behaviors as demonstrated by the reduction in number of cigarettes per day and carbon monoxide (CO) levels. On the other hand, 0.3 mg cigarettes led to an increase in cigarette per day and in CO. Both cigarette types led to significant reductions in cotinine levels. The 0.05 mg cigarettes and nicotine lozenge were associated with reduced carcinogen exposure. While no increases were observed for carcinogen exposure with the 0.3 mg nicotine cigarette, the only significant decrease occurred for total NNAL. No significant changes were observed for cardiovascular measures. Both 0.05 mg nicotine cigarettes and nicotine lozenge were associated with reduced nicotine dependence and no increase in product withdrawal scores, whereas the 0.3 mg nicotine cigarettes resulted in no change in nicotine dependence and an increase in withdrawal scores upon cessation. The 0.05 mg cigarette was associated with greater relief of withdrawal from usual brand cigarettes than the nicotine lozenge. The 0.05 mg cigarette led to a significantly higher rate of cessation than the 0.3 mg cigarette and a similar rate as nicotine lozenge [2].

A similar study conducted by the same group where experimental conditions were: 1) 0.05 to 0.09 mg nicotine yield cigarettes (Quest and Xodus); 2) 0.05 to 0.09 mg nicotine yield cigarettes (Quest and Xodus) plus nicotine patch; and 3) 21 mg nicotine patch. In the two conditions that involved very low nicotine content cigarettes, the results showed a reduction in number of study cigarettes smoked, levels of alveolar carbon monoxide levels, total nicotine equivalents and total NNAL, and a reduction in perceived risk for addiction. Upon cessation of the study products, significant increases in craving and changes in withdrawal symptoms were observed for all three conditions, with no significant differences across conditions[3].

Another research group conducted three studies using reduced nicotine content cigarettes. The three studies were: 1) a single cigarette crossover, comparing cigarettes of different nicotine content and yield; 2) a 6 week tapering study, where nicotine yields were decreased on a weekly basis; 3) a similar tapering study in which nicotine yields were decreased on a monthly basis. All studies found: 1) Systemic intake of nicotine reflected the nicotine content of the cigarettes, with only small degrees of compensation. That is, as nicotine content declined, nicotine intake declined proportionally; 2) No evidence of increased systemic exposure to carcinogens (NNAL; polycyclic hydrocarbons) with decreasing nicotine content; 3) No evidence of changes in biomarkers of cardiovascular disease with decreasing nicotine content[4-6]. The mean level of education in participants was college graduation (e.g. ~15-16 years of education) and nearly all subjects were white.

2.3. Study Rationale

Reducing the nicotine content in cigarettes to levels that are not reinforcing or addictive is considered a feasible national policy to reduce tobacco-related morbidity [7]. When considering a national policy, it is necessary to consider that the single greatest predictor of tobacco use is low SES [8, 9]. In a report to the Tobacco Related Disease Research Program (TRDRP) of California, a review of the literature showed that persons of low income, education, unemployed, working-class jobs, or living in medically underserved areas have the highest smoking rates [10]. The Centers for Disease Control reported that the adult smoking rate was 31% below the federal poverty level compared to 19% at or above the poverty level [11].

These differences are even more pronounced in women. Tobacco advertising and marketing practices target low socioeconomic populations. Low SES smokers have less financial access to standard of care treatment for nicotine dependence such as nicotine pharmacotherapy and are less likely to quit despite having similar quit attempts as high income smokers. While it has long been thought that Federal excise taxes are more likely to reduce smoking in low income smokers, recent data indicate that low SES smokers are not more likely to quit than higher income smokers, and thus bear a disproportionate percent of their income on cigarette taxes [12].

Low SES smokers also exhibit a greater degree of cigarette brand loyalty. The disparities in smoking rates between low SES and high SES are projected to be even greater in the future [13]. The incidence rate of tobacco-related cancers has been significantly higher in low SES smokers compared to higher SES smokers [14] even after adjustment for cigarettes per day [15-22]. This difference is likely accounted for by higher levels of nicotine dependence and associated toxin intake in low SES smokers. Lower levels of education are associated with higher levels of cotinine per cigarette smoked in the National Health and Nutrition Examination Survey (NHANES) and other data [23, 24]. This may reflect low income smokers' preference for higher nicotine yield cigarettes [14].

Smoking rates are higher in both low SES whites and blacks. Because blacks largely prefer mentholated cigarettes whereas whites predominantly smoke non-menthol brands, research on tobacco harm in blacks has focused on whether menthol is more dangerous than non-menthol cigarettes in terms of disease risk or nicotine dependence. Under section 907 (e) of the 2009

Family Smoking Prevention and Tobacco Control Act (FSPTCA), the FDA's Tobacco Products Scientific Advisory Committee (TPSAC) submitted a report to the Secretary of Health and Human Services (HHS) on the public health impact of mentholated cigarettes. The TPSAC concluded that menthol doesn't increase cancer risk relative to non-mentholated cigarettes. We showed that cotinine levels did not differ significantly between menthol and non-menthol smokers [25, 26]. The TPSAC recommended that removal of menthol from the marketplace would benefit public health, based on the high use of menthol cigarettes as a starter product in youths. Since most data indicate that menthol is unrelated to cotinine levels among smokers of commercially available cigarettes, the greater degree of nicotine dependence in blacks may reflect their higher representation in low SES populations. The FDA has not yet acted on the TPSAC recommendation. It is possible that menthol may affect nicotine uptake in smokers of RNC cigarettes.

The FSPTCA is based on the premise that making tobacco less or non-addictive will result in a reduction in harm from tobacco smoke [27, 28]. This premise would apply for all aspects of nicotine dependence including smoking onset in non-addicted youths and smoking cessation in current dependent smokers. Although it is well known that compensatory smoking behavior (e.g. more frequent puffs or inhaling deeper) limits the ability to reduce nicotine exposure, at least in commercially available higher nicotine cigarettes [29], the feasibility of progressively switching to low nicotine cigarettes was considered to be technically feasible by the American Medical Association and other authoritative groups [28, 30]. A broad-based policy needs to consider the diverse population of smokers who vary substantially by socio-demographic, economic and cultural factors that may affect nicotine dependence and the choice of tobacco products smoked. In an initial report by Benowitz et al. [4] of a randomized trial of a specially blended low nicotine cigarette with features similar to Marlboro brand cigarettes, 130 smokers progressively lowered their nicotine over a 6-month period. There was a concurrent decrease in exposure to nicotine or nicotine derived carcinogen biomarkers such as cotinine and NNAL. In this trial, the mean level of education in participants was college graduation (e.g. ~15-16 years of education) and nearly all subjects were white. A similar trial by Hatsukami et al. [2] of 165 smokers that used commercially available Quest cigarettes assigned to two different low nicotine cigarettes for 6 weeks had similar findings.

A potential policy measure of lowered nicotine exposure through reduced nicotine yield cigarettes needs to specifically address whether lowered nicotine tobacco products reduces nicotine exposure given that smokers undertake compensatory smoking behaviors to maintain constant nicotine intake. The policy also requires that reduced nicotine cigarettes not increase exposure to tobacco smoke toxins and carcinogens, as well as decrease the levels of physiological dependence and smoking behaviors associated with nicotine dependence. This needs to be documented prior to the full endorsement of the policy [28] and will be the major focus of this proposal.

Stress is the major reason why youths and adults smoke. Cigarette smokers report that cigarettes help them calm down and relax. However the relationship between stress and smoking is still not well understood. Nicotine increases physiological stress through activation of the hypothalamic-pituitary-adrenal (HPA) axis, producing the stress hormone cortisol. Studies indicate that smokers have higher salivary levels of cortisol throughout the day than nonsmokers (Figure 1, data from: Steptoe A et al. [31]). Cortisol is also elevated in adults with lower SES compared to higher SES adults, although the findings are not consistent [32]. Although smokers report immediately after smoking that they have reduced stress, the response is acute and may reflect a temporary relaxed state while taking a break. Studies show that within half an hour after smoking, reported psychological stress levels in smokers return to their normal high levels [33]. This is supported by data showing that quitters have reduced psychological stress levels compared to persons who continue to smoke [34]. In the current study, we suggest that an important endpoint in a reduced nicotine policy for all smokers, but particularly for low SES

smokers, is that physiological and psychological stress should not be increased but decreased in a reduced nicotine regimen. An assessment of whether the gradual reduction in nicotine content of cigarettes is associated with a reduction in stress is the major focus of Specific Aim 3 of this proposal.

In studying how different cigarettes affect nicotine dependence, cotinine is the most commonly used biomarker of nicotine uptake and exposure. It is easily measured by ELISA and discriminates with a high degree of precision exposure to mainstream smoke vs. environmental tobacco smoke. It is also used as a general marker of the dose of exposure. However, cotinine represents <15% of total urinary nicotine metabolites. Because the rate of nicotine metabolism varies among individuals and is associated with the degree of nicotine dependence, the genotypic and phenotypic variation of nicotine metabolism will likely be an important factor in determining in which smokers a nicotine reduction strategy might be successful. Examining metabolic phenotypes as predictors of participant drop-out/relapse will be the major focus of Specific Aim 2 of this proposal.

3. Inclusion and Exclusion Criteria

3.1. Inclusion Criteria

1. Age 18-65
2. Less than Bachelor's degree
3. Smoke >4 cigarettes/day for at least a year
4. Willing to smoke one flavor of cigarette during the trial (menthol or non-menthol)
5. Read and write in English
6. Able to understand and consent to study procedures
7. Plan to live in the local area for the next 8 months
8. Women not pregnant or nursing and taking steps to avoid pregnancy
9. No quit attempt in the past month and not planning to quit in the next 6 months (ensuring stability of smoking).
10. Ability to consistently receive phone calls over the next 8 months
11. Participants who become prisoners or otherwise subject to correctional supervision through probation, parole, home confinement, electronic monitoring, work release or other monitored, non-custodial supervision after signing the consent form.

    Notes Related to Prisoner Participation

    - The prisoner participant must be permitted by their probation/parole officer, court or other supervising authority to go to the research office visits, and the devices need to be programmed to reflect that additional time/place of travel. These issues will be resolved by the prisoner and their supervising authority on a case-by-case basis.

    Rationale to include prisoners: Potential benefit of the subject (intent and reasonable probability of improving the health or well-being of the subject)

3.2. Exclusion Criteria

1. College graduate
2. Currently pregnant or nursing
3. Systolic blood pressure greater than or equal to 160
4. Unstable or significant medical condition such as COPD or kidney failure that is likely to affect biomarker data
5. Use of non-cigarette nicotine delivery product in the past week (included cigars, pipes, chew, snus, hookah, e-cig, and marijuana)

6. Currently reducing or planning to reduce cigarette consumption in the next month
7. Use of smoking cessation medicine in the past month
8. History of difficulties providing blood samples; fainting, poor veins, anxiety, etc.
9. Regular use (more than weekly) of illegal drugs or prescription drugs used for non-medical purposes in the past 3 months or inpatient treatment for these in the past 6 months.
10. Uncontrolled serious psychotic illness (includes schizophrenia, bipolar disorder, eating disorder, and dementia) or inpatient treatment for a mental health condition in the last 6 months
11. Alcohol abuse that would hinder the participant's ability to participate
12. Significant medical condition i.e. stroke, MI, cancer in the last month
13. Other members of the household are currently participating in a trial related to reduced nicotine cigarettes
14. Taking an out of town trip or vacation in the next 8 months that will last 3 weeks or more or has major surgery planned in the next 8 months
15. Any other condition or situation that would, in the investigator's opinion, make it unlikely that the participant could comply with the study protocol
16. Participants who are prisoners at time of enrollment
17. Participants who become custodial inmates at any correctional facility after enrollment in the research.

3.3. Early Withdrawal of Subjects

3.3.1. Criteria for removal from study

Participant withdrawal prior to randomization (Baseline Phase I and II)
These two phases are designed to identify participants who are not able or willing to comply with the full study protocol. During Baseline I, participants will smoke their own usual brand of cigarettes for 1 week. At Baseline II, all participants will be asked to smoke research cigarettes with a normal amount of nicotine. Participants who are removed during these two phases will be replaced prior to randomization until a total of 200 participants have been randomized (same for George Washington University).

Those who are not compliant with the study protocol prior to randomization for any of the following reasons will be withdrawn from the study **either during Baseline Phase I or Phase II**:

1. **Participant reports using any non-cigarette nicotine products at more than one visit.** Includes cigars, pipes, snuff, chew, hookah, electronic cigarette, marijuana, or any other illegal smoked substance, or any other nicotine containing product.

Those who are not compliant with the study protocol prior to randomization for any of the following reasons will be withdrawn from the study **during Phase II only**:

1. **Participant consumes more than 10% of cigarettes consumed are non-research cigarettes** in the 6 days prior to visit 3 only (Average cigarettes from day 15-20, e.g. 4 or more out of 30 cigarettes in 6 days for a 5 CPD smoker; 18 or more out of 180 cigarettes in 6 days for a 30 CPD smoker).
2. **Participant has reduced their cigarette consumption by more than 50% compared to baseline cigarettes per day** (when cigarettes per day are averaged over days 15-20) **because of non-compliance. This does not include situations of illness or other circumstances that would interfere with the participants' normal smoking behavior**.

Participant withdrawal at any point during the study if any of the following occurs:

1. **New pregnancy:** Participants who report a new pregnancy at any point during the study will be withdrawn or confirmed by urinary pregnancy test.
2. **Cardiovascular disease (CVD) event:** 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).
3. **DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system)**.
4. **Participant choice:** Participants may choose to remove themselves from the study by informing the research team in writing or verbally at any point during the study.

The following will be monitored and can lead to the participant being withdraw at any point by the PI:

1. **Expired breath carbon monoxide increase:** If the average of two consecutive CO measurements in the same visit is
    i. CO is greater than 50 ppm if CO at baseline visit 1 is <20 ppm.
    ii. CO is greater than 60 ppm if CO at baseline visit is 1 20 – 34 ppm.
    iii. CO is greater than 70 ppm if CO at baseline visit is 1 35 – 49 ppm.
    iv. CO is greater than 80 ppm if CO at baseline visit is 1 50 – 60 ppm.
    v. CO is greater than 90 ppm if CO at baseline visit is 1 61 – 70 ppm.

    If the average of the two readings is still out of range after testing twice, an AE will be documented and the participant will be monitored by the medical professional.
2. **Cigarette per day increase:** The average CPD increases by more than 100% from the average CPD at the baseline assessment visit.
3. **Increase Systolic Blood Pressure** over >160 mmHg
4. **Increased substance abuse** in which the participant is behaving inappropriately at visits or demonstrates an inability to continue with the study.
5. **Any 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.
6. **Any Missed visits** where the participant would have received new research cigarettes. Of concern is what type of cigarettes (research or own brand) the participant has been smoking if they did not attend a visit where they would have received research cigarettes. Participants will be reviewed and considered for withdrawal on a case by case basis.
7. **Any situation where participant is not able to smoke research cigarettes for a period of more than 2 weeks**
8. **Participant behavior:** If a participant is behaving in an inappropriate or threatening manner, demonstrates an inability to continue with the study, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, etc., then the PI can withdraw him/her from the study at the PI's discretion.
9. **Significant baseline smoking rate increase:** A participant may be withdrawn from the study if they meet **BOTH** of the following criteria (only if receiving research cigarettes):
    a. **Cigarette per day increase:** The average CPD increases by more than 100% from the average CPD at the baseline assessment visit

b. **Expired breath carbon monoxide increase:** If the average of two consecutive CO measurements in the same visit is:
   i. CO is greater than 50 ppm if CO at baseline visit 1 is <20 ppm.
   ii. CO is greater than 60 ppm if CO at baseline visit 1 is 20 – 34 ppm.
   iii. CO is greater than 70 ppm if CO at baseline visit 1 is 35 – 49 ppm.
   iv. CO is greater than 80 ppm if CO at baseline visit 1 is 50 – 60 ppm.
   v. CO is greater than 90 ppm if CO at baseline visit 1 is 61 – 70 ppm.

3.3.2. Follow-up for withdrawn subjects

Subjects are withdrawn if they provide a verbal or written request to be removed from the study at any time after the initial consent. All data collected up to the withdrawal date will be included in the analysis of the data with Intent to Treat statistical rules. If a subject consents but is not randomized, or is consented but does not complete the baseline evaluation and assessments, the subject will be replaced. Subjects who withdraw themselves will be asked to complete a questionnaire (named End of Trial Questionnaire in Appendix of Coordinator entered Surveys) regarding the reasons for dropping out. Subjects that were selected to use a topography machine (see below) will be asked to use the machine for 1 additional day.

4. Recruitment Methods

4.1. Identification of subjects

We will do general recruitment in our catchment area to identify smokers. All recruitment for this study will be routed through IRB Protocol #2213 which will also serve as the initial recruitment point of contact.

In addition, Dr. Ping Du will identify smokers in the Hershey Medical Center HIV/AIDS outpatient clinics. In previous research the smoking prevalence in HIV+ people ranges from 40-70% [35], depending on the populations and the study designs. The smoking prevalence in our HMC HIV+ patients is 44%. In clinical practice, HIV-infected people are seeking regular HIV primary care and evaluate immune status (measured by their CD4 count and HIV viral load) every 6 months. A clinic-based approach will be utilized to recruit a consecutive sample of 30 HIV+ smokers from Hershey Medical Center HIV/AIDS outpatient clinics for participation in the trial. Dr. Du will oversee the recruitment process and answer questions about this study from HIV+ patients. The HMC HIV/AIDS outpatient clinics provide HIV care and are familiar to the potential participants. Dr. Du will work with the clinic to review daily patients' roster prior to clinic visits to identify HIV+ smokers. A study flyer will be posted at the HIV/AIDS clinics and be provided to all HIV+ patients during their routine HIV care visits. HIV+ smokers who are interested in participating in this study will contact the study coordinator to screen for their eligibility using the Project Screener 1.

4.2. Recruitment process

This will be a randomized trial of cigarette smokers (n=400 with an expected dropout rate of 30% for a total of 280 smokers) recruited at two sites: Pennsylvania State University (n=200) and George Washington University (n=200). Recruitment materials will direct cigarette smokers to contact the study center by telephone or visit the Penn State TCORS website to complete the basic eligibility screener also called the Call routing screener- IRB protocol STUDY00002213). Once they complete this screener and they are eligible for one of our studies, they will be forwarded to the appropriate study coordinator for further screening.

4.3. Recruitment materials

All our general recruitment materials have been included under the IRB protocol STUDY00002213. They include flyers (with the header "Do you smoke" and the study center's number listed below), radio advertisement script, and a letter to past participants.

In the HIV clinic, a study flyer will be posted and handed to potential participants that gives them information on the study (uploaded in Recruitment materials named Recruitment Letter to Clinic Participants).

4.4. Eligibility/screening of subjects

The Penn State Tobacco Center of Regulatory Science grant includes several projects that are recruiting smokers with similar, but not identical characteristics. In order to be efficient with recruitment and avoid confusion in the community, we will advertise one single study website and phone number where potential participants can go to obtain information on studies being conducted by TCORS primary investigators. Participants who are interested in the studies will complete the following screening process:

1. **Call Routing Screener-** IRB protocol STUDY00002213 **(either over the phone or on TCORS website):** This questionnaire is designed to identify the most common characteristics needed to participate any of the TCORS studies. An algorithm will be set up in REDCap that will deem them eligible for the appropriate study based off of their answers and inform the appropriate study coordinator from each project when a participant has completed the screener. They will leave information to be contacted by a study coordinator.

2. **Project Screener 1:** Once a participant has passed the Call Routing Screener, the appropriate study coordinator will conduct a second screening over the phone which will be more specific to their study. If the participant passes the second screener then a study visit (Screening /Assessment Visit 1) will be scheduled at PSH Clinical Research Center. Participants will verbally consent to their information being retained and being contacted for future studies. A full script and screening questions for this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

3. **Project Screener 2:** The participant will go through this last screener at their Screening /Assessment Visit 1at the PSH Clinical Research Center. This screener will also have a review of the first and second screener to make sure nothing has changed since the coordinator last spoke with the participant. A full script and screening questions for this study are in the "Consent Forms and Recruitment Materials" section of the IRB application.

5. Consent Process and Documentation

5.1. Consent Process

5.1.1. Obtaining Informed Consent

1. Timing and Location of Consent

When participants attend their first in person visit, they will have the study explained to them in detail, have the opportunity to ask questions and then be asked to sign the consent form. Participants will be given a signed copy of

the form. This will take place in a private clinic room at the Penn State Hershey Clinical Research Center.

2. Coercion or Undue Influence during Consent

Recruitment materials for the study will be broadly distributed throughout the community. Once participants contact the study center, 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 enrollment in the trial is purely voluntary and the researchers will not offer comments about whether they believe the participant should enroll in the study or not. Given the number of contacts and visits involved in the study protocol, the compensation provided to the participant is modest.

5.1.2. Waiver or alteration of the informed consent requirement

N/A

5.2. Consent Documentation

5.2.1. Written Documentation of Consent

An IRB approved, stamped consent form will be used to document consent. Both the researcher and the participant will retain a copy of the consent.

5.2.2. Waiver of Documentation of Consent

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

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

5.3. Consent – Other Considerations

5.3.1. Non-English Speaking Subjects

Non-English speaking subjects will not be eligible for this study because it is essential for assessing their experience with the protocol during study contacts (i.e. telephone interviews) and some of our measures are not validated in other languages.

5.3.2. Cognitively Impaired Adults

Cognitively impaired adults will not be eligible for this study.

1. Capability of Providing Consent

N/A

2. Adults Unable To Consent

N/A

3. Assent

N/A

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

Children will not be eligible for this study.

1. Parental Permission

N/A

2. Assent

N/A

6. 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:

☒ Authorization will be obtained and documented as part of the consent process.

☐ 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)*

☐ Full waiver is requested for entire research study *(e.g., medical record review studies)*

☒ Alteration is requested to waive requirement for written documentation of authorization

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

1. Plan to protect PHI from improper use or disclosure

All data collected during the screening process will be directly entered into REDCap.

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 be practicably be conducted without access to and use of PHI

N/A

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 in the study.

6.3. Waiver or alteration of authorization statements of agreement

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

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

Access to the information will be limited, to the greatest extent possible, within the research team.

All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7. Study Design and Procedures

7.1. Study Design

This will be a two-arm randomized double-blinded trial. The study will proceed in four phases.

1. In Baseline Phase 1, subjects will smoke their own usual brand of cigarettes for 1 week to get acclimated to study participation.
2. In Baseline Phase 2, participants will be assigned (unblinded) to use research cigarettes that contain the normal amount of nicotine of conventional store bought cigarettes and matched on the participants' menthol flavor preference (menthol or non-menthol) for 2 weeks. Participants who complete this 2 week period of smoking research cigarettes and agree to continue with the study will enter the Randomized Double-Blind Phase.
3. During Randomization Phase 3, participants will be randomized to either:
    a. continue to smoke the same research cigarettes for a further 18 weeks
    b. switch to progressively reduced nicotine content (RNC) cigarettes over the next 18 weeks
4. Finally, during Treatment Choice Phase 4, both groups will then be offered the choice to:
    a. return to their usual brand
    b. Receive assistance to quit smoking (with counseling and FDA-approved medication provided at no cost for 11 weeks)

Table 1: Dosing Schedule for smokers enrolled in the study prior to 12/19/16

Phase:	**Baseline I**	**Baseline II**	**Randomized Double-Blind Phase**					**Treatment Choice Phase****
Wks/Phase:	**1**	**2**	**3**	**3**	**3**	**3**	**6**	**12**
Cigarette type:	Own Brand	Usual Nicotine Research Cigarettes	Reduced Nicotine Step 1	Reduced Nicotine Step 2	Reduced Nicotine Step 3	Reduced Nicotine Step 4	Reduced Nicotine Step 5	Variable
	Nicotine content (mg/cigarette)†							
regular: **RNC** *menthol:*	Around 11mg	11.0 12.1	7.8 7.0	3.2 3.4	1.3 1.4	0.7 0.7	0.2 0.2	Variable
regular: **UNC** *menthol:*	Around 11mg	11.0 12.1	11.0 12.1	11.0 12.1	11.0 12.1	11.0 12.1	11.0 12.1	Variable*

*Menthol smokers randomized to the UNC treatment group who choose to stay on study cigarettes will switch to a 9.9 mg or 12.1 mg cigarette type determined by the time of entry into the study due to a 12.1 mg menthol study cigarette supply shortage. A consent form addendum will be filled out for all menthol smokers who choose to stay on study cigarettes in the Treatment Choice Phase.

Table 2: Dosing Schedule for smokers enrolled 12/19/16 or after

Phase:	**Baseline I**	**Baseline II**	**Randomized Double-Blind Phase**					**Treatment Choice Phase****
Wks/Phase:	**1**	**2**	**3**	**3**	**3**	**3**	**6**	**12**
Cigarette type:	Own Brand	Usual Nicotine Research Cigarettes	Reduced Nicotine Step 1	Reduced Nicotine Step 2	Reduced Nicotine Step 3	Reduced Nicotine Step 4	Reduced Nicotine Step 5	Variable
	Nicotine content (mg/cigarette)†							
regular: **RNC** *menthol:*	Around 11mg	11.0 9.9	7.8 7.0	3.2 3.4	1.3 1.4	0.7 0.7	0.2 0.2	Variable
regular: **UNC** *menthol:*	Around 11mg	11.0 9.9	11.0 9.9	11.0 9.9	11.0 9.9	11.0 9.9	11.0 9.9	Variable

**As of the approval date of the June 7th 2017 version of the protocol, smokers entering the treatment choice phase will not be given the option to stay on research cigarettes.

†Nicotine contents are based on an estimated 0.7 g tobacco content per cigarette and nicotine concentrations (mg/g) from Richter et al. (2016)[36]

7.2. Study Procedures

7.2.1. Baseline Phase I- Orientation/Assessment Visit and Visit 1 (Day 0)

1. Administer Project Screener 2
2. Informed Consent will be taken in a private clinic room in the CTSI.
    a. Explain study protocol, use and description of cigarettes, and outcome measures. Participant (P) will have adequate time to review the consent form and ask any questions. Two consent forms will be signed, one will be left at the clinic and one will be taken with the participant.

3. Give the P the Study Overview Participant Handout (uploaded in Supporting Documents named Study Overview Participant Handout)
4. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
5. Complete medical history, NIDA drug screen, and concomitant medications forms and blood pressure measurement will be completed to confirm eligibility (all questionnaires (Q) are uploaded in Supporting Documents section).
6. Research staff will take heart rate (HR), weight, height, and waist:hip ratio measurements. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
7. If P meets all inclusion criteria the coordinator will proceed with the rest of the baseline questionnaires below (all questionnaires are uploaded in Supporting Documents named Appendix of Coordinator entered Surveys and Appendix of Subject entered surveys):
    1. Demographics
    2. Tobacco Use History
    3. Butt out Q.
    4. Cigarette Details
    5. Nicotine Dependence Q.
    6. WI Prepare
    7. Cigarette Liking scales
    8. Revised MN Withdrawal Scale
    9. Questionnaire on Smoking Urges
    10. Centers for Epidemiological Studies (CESD)
    11. Perceived Stress Q.
    12. Kessler 6
5. Explain to P that they will smoke their current brand of cigarettes as usual for the next week. Compliance with the study protocol including not using other forms of tobacco or marijuana will be stressed. Participants will also be asked to honestly report any other tobacco or marijuana use at subsequent visits.
6. The study coordinator will give out and explain to P how to fill out the daily cigarette diary (in Supporting Documents section). They will be instructed to use this every day to tally their cigarettes smoked. They will also be asked to circle in their diary any non-research cigarettes that they smoke so that we can record this at subsequent visits.
7. A subset of 100 P (50 each arm) will be asked to provide 4 saliva samples throughout the course of the day before they come into the next clinic visit to look at Cortisol (stress biomarker). They will be given a kit with instructions on collection and will watch an instructional how-to video (uploaded in Supporting Documents). To collect a saliva sample Ps will place a cotton swab under their tongue for 2 minutes. They will repeat this 4 more times throughout the day. Ps will be asked to complete a cortisol log on the day they take the cortisol saliva samples. The log will be provided in the kit with the collection tubes. It will provide instructions on how to take the samples along with dates and times for each sample that was collected. Additional questions in the log address possible interactions with cortisol such as, stress events, alcohol consumption, and exercise. Once they are done collecting the samples for the day they will keep them in the refrigerator until it is time to bring them to the clinic visit the next day.
8. A randomly selected subset of 100 Ps will be asked to use the Smoking Puff Analyser-Mobile (SPA-M) (SODIM, France) smoking topography device which mechanically records measures of smoking (e.g. number of puffs, puff velocity, puff duration, interpuff interval, puff volume) for baseline topography assessment. The P will smoke through a

plastic mouthpiece connected by a plastic tube to a handheld, portable device with a pressure transducer. Ps will be instructed on how to use the device and will be given an instructional handout for reference. They will also watch an instructional how-to video (uploaded in Supporting Documents). They will be asked to smoke all of their cigarettes as they normally do with the device for next two days after the visit. Participants who are selected to use the device will collect cigarette butts for one day while using the device and collect cigarette butts from one day while not using the device. Instructions (uploaded in Supporting Documents) and storage bags to collect the butts will be given. They will bring the butts back at their next visit.

9. The next study visit will be scheduled for one week later at approximately the same time. They will receive a print out of their next study visits and phone calls.

7.2.2. Baseline Phase I- Visit 2 (Day 7)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. P will give a blood sample taken by the Research staff in the CTSI clinic room. Blood biosamples will be used to look at the following (some biomarkers will be analyzed in selected subgroups of collected samples):
    1. Nicotine metabolites (nicotine, cotinine, 3HC)
    2. Blood glutathione (GSH) and glutathionylated proteins (GSSP)
    3. Bilirubin
    4. Creatinine
    5. Hemoglobin
    6. High-sensitivity c-reactive protein (hs-CRP)
    7. Interleukin-6 (IL-6)
    8. DNA
3. P will give a urine sample. Urine biosamples will be used to look at the following (some biomarkers will be analyzed in selected subgroups of collected samples):
    1. Nicotine metabolites (nicotine, cotinine, 3HC)
    2. Tobacco specific nitrosamines (NNAL,NNK)
    3. Polycyclic Aromatic Hydrocarbons (1-Hydroxypyrene,)
    4. Oxidative stress biomarkers (8-OHdG, F2-isoprostanes)
    5. Creatinine
    6. Total solids
    7. VOC biomarkers (mercapturic acids)
    8. Menthol
4. Adverse events trigger questions (uploaded in Supporting Documents)
5. Collect daily cigarette diaries from previous visit.
6. Collect saliva samples and log from selected Ps.
7. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use will be asked to use the device for the next two days after the clinic visit. If for some reason the participant was not able to complete collecting topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
8. P will complete the following questionnaires
    1. Every Visit Form
    2. Tobacco and Marijuana use/daily cigarette log
    3. Concomitant Medications
    4. Audit- C (current alcohol consumption)
    5. Environmental Tobacco Smoke Q.
    6. Menthol Q.

7. Clinical COPD Q
8. Nicotine Dependence Q.
9. WI Prepare
10. Perceived Health Risks
11. Cigarette Liking scales
12. Revised MN Withdrawal Scale
13. Questionnaire on Smoking Urges
14. Centers for Epidemiological Studies (CESD)
15. Perceived Stress Q.
16. Kessler 6
17. Social Support Q.

9. P will be given research cigarettes that contain the normal amount of nicotine of conventional cigarettes and matched on the participants' menthol flavor preference (menthol vs. non-menthol). They will receive enough research cigarettes that will last them for 2 weeks at a 150% of their baseline reported cigarettes. They will be instructed to smoke as they normally do with the test cigarettes for the next 2 weeks.
10. The study coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
11. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
12. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
13. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
14. The next study visit will be scheduled for 2 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

7.2.3. Baseline Phase II- Phone Survey 1 (Day 14)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

7.2.4. Baseline Phase II- Visit 3 (Day 21)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.

5. Adverse events trigger questions
6. Collect daily cigarette diaries and research cigarette packs (unopened, opened or empty) from previous visit.
7. Collect smoking topography device and cigarettes butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use for the next 2 days after the clinic visit. If for some reason the participant was not able to complete collecting topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
8. Collect saliva samples and log from selected Ps.
9. P will complete the following questionnaires
    1. Every Visit Form
    2. Tobacco and Marijuana use/daily cigarette log
    3. Concomitant medications
    4. Environmental Tobacco Smoke Q.
    5. Menthol Q.
    6. Clinical COPD
    7. Nicotine Dependence Q.
    8. Cigarette Liking Scale
    9. Perceived Health Risks
    10. Revised MN Withdrawal Scale
    11. Questionnaire on Smoking Urges
    12. Centers for Epidemiological Studies (CESD)
    13. Perceived Stress Q.
    14. Kessler 6
10. At this visit Ps will be evaluated for inclusion in the randomization phase based on the withdrawal criteria in Section 3.3.
11. Ps who continue to the randomization phase will be randomized to either receive the Same Nicotine Content (SNC) or the Reduced Nicotine Content (RNC) cigarettes. P will receive enough research cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes per day. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks.
12. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
13. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
14. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
15. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
16. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

7.2.5. Randomization Phase- Phone Survey 2 (Day 28)

1. Ask P the following questionnaires:
    - **a.** Tobacco and Marijuana use/daily cigarette log
    - **b.** Revised MN Withdrawal Scale
    - **c.** Questionnaire on Smoking Urges
    - **d.** Cigarette Liking Scale

e. Smoking Device Log (if applicable)

2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

6. Randomization Phase - Visit 4 (Day 42)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. P will give a blood sample taken by the Research staff in the CTSI clinic room.
3. P will give a urine sample.
4. Adverse events trigger questions.
5. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
6. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use for the next 2 days after the clinic visit. If for some reason the participant was not able to complete collecting topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
7. Collect saliva samples and log from selected Ps.
8. P will complete the following questionnaires
    1. Every Visit Form
    2. Tobacco and Marijuana use/daily cigarette log
    3. Concomitant medications
    4. Environmental Tobacco Smoke Q.
    5. Menthol Q.
    6. Clinical COPD
    7. Nicotine Dependence Q.
    8. Cigarette Liking Scale
    9. Revised MN Withdrawal Scale
    10. Questionnaire on Smoking Urges
    11. Centers for Epidemiological Studies (CESD)
    12. Perceived Stress Q.
    13. Kessler 6
9. P will be given the test cigarettes. They will receive the test cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks
10. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
11. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
12. P will be given the Daily cigarette diary and be instructed to use this every day to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
13. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
14. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

7. Randomization Phase- Phone Survey 3 (Day 49)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

8. Randomization Phase - Visit 5 (Day 63)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.
5. Adverse events trigger questions.
6. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
7. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use for the next 2 days after the clinic visit. If for some reason the participant was not able to collect the topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
8. Collect saliva samples and log from selected Ps.
9. P will complete the following questionnaires
   1. Every Visit Form
   2. Tobacco and Marijuana use/daily cigarette log
   3. Concomitant medications
   4. Environmental Tobacco Smoke Q.
   5. Menthol Q.
   6. Clinical COPD
   7. Audit-C
   8. Nicotine Dependence Q.
   9. Cigarette Liking Scale
   10. Revised MN Withdrawal Scale
   11. Questionnaire on Smoking Urges
   12. Centers for Epidemiological Studies (CESD)
   13. Perceived Stress Q.
   14. Kessler 6
10. P will be given the test cigarettes. They will receive the test cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks.
11. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.

12. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
13. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
14. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
15. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

9. Randomization Phase- Phone Survey 4 (Day 70)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

10. Randomization Phase - Visit 6 (Day 84)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. P will give a blood sample taken by the Research staff in the CTSI clinic room.
3. P will give a urine sample.
4. Adverse events trigger questions.
5. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
6. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use for the next 2 days after the clinic visit. If for some reason the participant was not able to complete collecting topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
7. Collect saliva samples and log from selected Ps.
8. P will complete the following questionnaires
   1. Every Visit Form
   2. Tobacco and Marijuana use/daily cigarette log
   3. Concomitant medications
   4. Environmental Tobacco Smoke Q.
   5. Menthol Q.
   6. Clinical COPD
   7. NIDA Drug Screen
   8. Nicotine Dependence Q.
   9. Cigarette Liking Scale
   10. Perceived Health Risks
   11. Revised MN Withdrawal Scale
   12. Questionnaire on Smoking Urges
   13. Centers for Epidemiological Studies (CESD)
   14. Perceived Stress Q.
   15. Kessler 6

9. P will be given the test cigarettes. They will receive the test cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks.
10. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
11. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
12. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
13. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
14. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

11. Randomization Phase- Phone Survey 5 (Day 91)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

12. Randomization Phase - Visit 7 (Day 105)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.
5. Adverse events trigger questions.
6. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
7. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions. Give the P the device back to use for the next 2 days after the clinic visit. If for some reason the participant was not able to complete collecting topography on the 2 days, we will ask them to make this time up at some point during the week. Give the P another set of cigarette butt collection bags to collect butts.
8. Collect saliva samples and log from selected Ps.
9. P will complete the following questionnaires
   1. Every Visit Form
   2. Tobacco and Marijuana use/daily cigarette log
   3. Concomitant medications
   4. Environmental Tobacco Smoke Q.

5. Menthol Q.
6. Clinical COPD
7. Stages of Change
8. Audit-C
9. Nicotine Dependence Q.
10. Cigarette Liking Scale
11. Revised MN Withdrawal Scale
12. Questionnaire on Smoking Urges
13. Centers for Epidemiological Studies (CESD)
14. Perceived Stress Q.
15. Kessler 6

10. P will be given the test cigarettes. They will receive the test cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks.
11. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
12. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
13. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
14. The selected Ps from Baseline I will be given saliva collection kits. P will be asked to perform the saliva collection protocol 4 times throughout the day before their next clinic visit and store them in the refrigerator until it is time to bring them to the clinic visit.
15. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

13. Randomization Phase- Phone Survey 6 (Day 112)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit, to complete and return the saliva samples (if applicable), and return cigarette packs (unopened, opened or empty) and topography device (if applicable).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

14. Randomization Phase - Visit 8 (Day 126)

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. P will give a blood sample taken by the Research staff in the CTSI clinic room.
3. P will give a urine sample.
4. Adverse events trigger questions.
5. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
6. Collect smoking topography device and cigarette butts from the selected Ps and remove data. Ask Device Log questions.
7. Collect saliva samples and log from selected Ps
8. P will complete the following questionnaires

1. Every Visit Form
2. Tobacco and Marijuana use/daily cigarette log
3. Concomitant medications
4. Environmental Tobacco Smoke Q.
5. Menthol Q.
6. Clinical COPD
7. Nicotine Dependence Q.
8. Cigarette Liking Scale
9. Revised MN Withdrawal Scale
10. Questionnaire on Smoking Urges
11. Centers for Epidemiological Studies (CESD)
12. Perceived Stress Q.
13. Kessler 6

9. P will be given the test cigarettes. They will receive the test cigarettes that will last them for 3 weeks at a 150% of their baseline reported cigarettes. P will be instructed to smoke as they normally do with the test cigarettes for the next 3 weeks.
10. The research coordinator will go over a study compliance protocol with the P. Compliance with not using non-research cigarettes, other forms of nicotine or tobacco, and marijuana will be stressed. The coordinator will complete the Compliance questionnaire that assesses the P's confidence in complying with the study procedures. Any confidence score 5 or lower will prompt the researcher to trouble shoot any problems with the P. This Q is uploaded in the Supporting Documents section.
11. Participants will be instructed to bring all cigarette packs (unopened, opened or empty) back to the study center at each study visit. This will allow the researcher to reconcile what was given out, smoked, and brought back and improve compliance.
12. P will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will also be asked to circle on their diary any non-research cigarettes that they may smoke so that we can record this at subsequent visits.
13. The next study visit will be scheduled for 3 weeks later at approximately the same time. They will receive a print out of their next study visits and phone calls.

15. Randomization Phase- Phone Survey 7 (Day 133)

1. Ask P the following questionnaires:
   - **a.** Tobacco and Marijuana use/daily cigarette log
   - **b.** Revised MN Withdrawal Scale
   - **c.** Questionnaire on Smoking Urges
   - **d.** Cigarette Liking Scale
   - **e.** Smoking Device Log (if applicable)
2. Remind P of next study visit and return cigarette packs (unopened, opened or empty).
3. P will receive $10 for completing phone survey and will receive it in check form that is mailed to their house.

16. Randomization Phase - Visit 9 (Day 147)

1. Research staff will take BP, HR, weight, waist:hip ratio. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.
5. Adverse events trigger questions.
6. Collect daily cigarette diarys and research cigarette packs (unopened, opened or empty) from previous visit.
7. P will complete the following questionnaires
   1. Every Visit Form

2. Tobacco and Marijuana use/daily cigarette log
3. Concomitant medications
4. Environmental Tobacco Smoke Q.
5. Menthol Q.
6. Clinical COPD
7. Stages of Change
8. NIDA Drug Screen
9. Audit-C
10. Butt out Q.
11. Nicotine Dependence Q.
12. WI Prepare
13. Cigarette Liking Scale
14. Perceived Health Risk
15. Revised MN Withdrawal Scale
16. Questionnaire on Smoking Urges
17. Centers for Epidemiological Studies (CESD)
18. Perceived Stress Q.
19. Kessler 6

8. All Ps will be given smoking cessation handouts and encouraged to quit. P will have 3 choices: quit and receive 11 weeks of nicotine gum/lozenges with brief cessation counseling (optional), continue to smoke the reduced nicotine cigarettes corresponding to the last type smoked for 12 more weeks at no cost, or switch back to their own brand of cigarettes at their own cost.
9.

a. <u>Participants who choose to make a quit attempt:</u>

These Ps will be offered an optional flexible smoking cessation treatment in which they will have the option to receive up to 11 weeks of short acting nicotine replacement therapy (gum or lozenges) at no cost and cognitive behavioral based smoking cessation counseling provided by study staff either in person or over the phone. Ps interested in quitting smoking must be willing to set a quit date one day before the week 22 visit (see Table 1 below). Ps will be given 6 day supply of the same research cigarette allocation that they received in Visit 8 to use until their quit date.

By this visit, some participants will have transitioned to smoking very low nicotine content research cigarettes. In order to select an appropriate nicotine replacement (NRT) dose, participants will be asked to quit smoking the day before their next visit (week 22). Participants will be encouraged to call the state telephone quit line and/or use the Freedom from Smoking (FFS) quit website (http://www.ffsonline.org/) to supplement the brief, in-person smoking cessation counseling sessions provided by study staff.

Table 1. Schedule of contacts for participants who choose to quit smoking during the Treatment Choice Phase 4

	Wk21 End randomized phase	-1d	Wk 22 Day 154	+1d	Wk 23 Day 161	Wk 24 Day 168	Wk 25 Day 175	Wk 26 Day 182	Wk 27 Day 189	Wk 28 Day 196	Wk 29 Day 203	Wk 30 Day 210	Wk 31 Day 217	Wk 32 Day 224	Wk 33 Day 231
In Person	X		X				X				X				

counseling session														
Telephone session				X	X				X				X		
Self guided session						X		X		X		X		X	
Quit day		X													
Possible NRT disbursement			X				X				X				
End of NRT use															X

b. <u>Participants who choose to switch back to their own brand:</u>

These Ps will have to purchase their usual brand of cigarettes at their own cost and not be given any more research cigarettes. Ps will be given the Daily cigarette diary and be instructed to use this everyday to tally their cigarettes smoked. They will not be asked to bring back their usual brand cigarette packs.

10. If the Ps go back to their usual brand, the next study visit will be scheduled for 4 weeks later at approximately the same time. They will receive a print out of their next study visits.
11. If the Ps chose to make a quit attempt they will be seen one week later. They will receive a print out of their next study visits and phone calls.

17. Treatment Choice Phase- Extra Visits for Participants Who Choose to Make a Quit Attempt- Week 22 (Day 154, +7)

At this visit participants will be evaluated by the researcher for nicotine withdrawal symptoms. If the participant chooses to use NRT, they will receive a 3 boxes of either nicotine gum (110 pieces/box) or lozenges (81 pieces/box) (according to participant's preference). At Penn State Hershey, NRT will be dispensed by the Penn State IDS. Adverse Events and concomitant medications will be assessed and a questionnaire (Smoking Cessation Quit Day) that includes the Minnesota Withdrawal Scale (MNWS) will be completed by the participant. Decisions about dosing will be determined based participant reported withdrawal symptoms. Participants who will have tapered to very low nicotine cigarettes should have minimal withdrawal symptoms and will require very low NRT dose. A general guideline for NRT Dosing will be used to make recommendations to participants as follows:

- Group 1:
  - Not able to remain abstinent or
  - Reports a score of 2 or more on the MNWS items #1 and #4 (irritable/ angry and/or craving to smoke)
- Group 2:
  - Able to remain abstinent and
  - Reported a score of 0 or 1 on MNWS items #1 and #4 or
  - had few slips

2mg Oral NRT (gum or lozenge) dosing guidelines for participants based on withdrawal symptom group allocation			
	Group	Max. number of pieces/day	Duration

Wk 22	1	1 piece as needed, not more than 1 every 1 hr or 16 in 24 hours	3 weeks
	2	1 piece as needed, not more than 1 every 4 hrs or 6 in 24 hours	3 weeks
Wk 25	1	1 piece as needed, not more than 1 every 2 hrs or 12 in 24 hours	4 weeks
	2	1 piece as needed, not more than 1 every 6 hrs or 4 in 24 hours	4 weeks
Wk 29	1	1 piece as needed, not more than 1 every 4 hrs or 6 in 24 hours	4 weeks
	2	1 piece as needed, not more than 1 every 8 hrs or 3 in 24 hours	4 weeks

The day after this visit, the researcher will call the participant to assess whether the participant is experiencing any side effects consistent with high nicotine levels and assess reducing the dose of NRT. If needed, additional courses of NRT will be given to the participant either at study visits or if the participant calls in to the study center to request additional NRT. At weeks 25 and 29 and the dosing schedule will be discussed with the participant. (See the Schedule of contacts for participants who choose to quit smoking during the treatment choice phase table above.)

General visit, phone, and self-guided sessions:
In addition to regular study visits (weeks 25 and 33), there will be two additional in person sessions (weeks 22 and 29), four phone sessions (weeks 22, 23, 27, and 31) and five self guided sessions. These additional phone and self-guided study sessions are not required part of the study. In order to avoid missed phone visits, researcher and participant will attempt to agree on a standing appointment, day and time. At each contact expired CO will be measured, adverse events and concomitant medications will be assessed and participants will complete questionnaires. Participants will receive 20 minutes (or less) of standard individual cognitive behavioral therapy (CBT) based on the *Freedom from Smoking* (FFS) curriculum (http://www.ffsonline.org/), from the American Lung Association. They will be given strategies to cope with triggers/urges to quit and when appropriate, the researcher will help the participant make a test call to the quitline and/or use the FFS website.

18. Treatment Choice Phase –Visit 10 (Day 175) All Participants

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.
5. Adverse events trigger questions.
6. If the P chose to continue smoking (usual brand) we will collect their diarys from their last visit.
7. P will complete the following questionnaires
    1. Every Visit Form
    2. Concomitant medications
    3. Environmental Tobacco Smoke Q.
    4. Menthol Q.

5. Clinical COPD
6. Revised MN Withdrawal Scale
7. Questionnaire of smoking urges
8. Centers for Epidemiological Studies (CESD)
9. Perceived Stress Q
10. Kessler 6
11. Non- Quitter Q. (non-quitters only)
12. Other Tobacco and Marijuana Use/Daily Cigarette Log (non-quitters only)
13. Dependence Q (non-quitters only)
14. Cigarette Liking Scale (non-quitters only)

8. Based off of the P's Treatment choice:
   a. Ps who want to quit will complete the Smoking Cessation Q and given NRT. They will go over strategies to cope with any triggers/urges to quit. Participants could be given a refill of NRT (3 boxes of gum or lozenge) as deemed appropriate by the researcher according to the participant's NRT usage and withdrawal symptoms.

   b. Ps who switch back to their own brand will not be given any research cigarettes. P will be given the Daily cigarette diary and instructed to use this every day to tally any usual brand cigarettes smoked.

9. If the Ps go back to their usual brand, the next study visit will be scheduled for 8 weeks later at approximately the same time. They will receive a print out of their next study visits.

19. Treatment Choice Phase – Visit 11 (Day 231)- All Participants

1. Research staff will take BP, HR, and weight. Exhaled CO will be taken by the research coordinator with the Pico+ Smokylzer by blowing into a tube.
2. Give pregnancy test for women childbearing age (have had a period in the past 12 months) and who have not had a hysterectomy for eligibility. Women will give a urine sample and the coordinator will perform a pregnancy urine test to see if it is positive or negative to confirm the eligibility criterion.
3. P will give a blood sample taken by the Research staff in the CTSI clinic room.
4. P will give a urine sample.
5. Adverse events trigger questions.
6. Collect daily cigarette diarys from previous visit.
7. P will complete the following questionnaires
   1. Every Visit Form
   2. Concomitant medications
   3. Environmental Tobacco Smoke Q.
   4. Clinical COPD
   5. Revised MN Withdrawal Scale
   6. Questionnaire of smoking urges
   7. Centers for Epidemiological Studies (CESD)
   8. Perceived Stress Q
   9. Kessler 6
   10. Other Tobacco and Marijuana Use/Daily Cigarette Log (non-quitters only)
   11. Dependence Q (non-quitters only)
   12. Cigarette Liking Scale (non-quitters only)
   13. Butt Out Q. (non-quitters only)

8. No further counselingor NRT will be given to the participants.

Between visits participants may be contacted by phone call, email, or text to remind them of upcoming study visits/phone calls or for study visit follow-up information (i.e. if the participant forgot their daily cigarette logs at their visit and we were collecting this information with them over the phone/email after their visit). Under Supporting Documents is the Appointment reminder email/letter that we will use to email or send the participant before Visit 1. The Appointment Card under Supporting Documents or a general calendar of the month will be given to participants at their visit to document future visits or when to use the smoking device or take saliva samples.

7.3. Duration of Participation

Subjects who complete all phases will participate in this study for 33 weeks.

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

7.4.1. Description

Experimental cigarettes from the NIDA Drug Supply Program (DSP; FDA Notice Number NOT-DA-13-002) will be used in this study. They are available from the Research Triangle Institute (RTI, North Carolina) with the same additives as commercial cigarettes but have varying levels of nicotine in them. The cigarettes come in either menthol or non-menthol cartons. Each carton includes 10 packs of cigarettes with 20 cigarettes per pack. Each carton is labeled with RTI barcodes, RTI log numbers, and batch/lot numbers. Cigarette packs do not have any labels.

7.4.2. Treatment Regimen

This will be a two-arm randomized double-blinded trial. The study will proceed in four phases.

1. In baseline Phase 1, subjects will smoke their own usual brand of cigarettes for 1 week to get acclimated to study participation.
2. In baseline Phase 2, all participants will then be assigned to use research cigarettes that contain the normal amount of nicotine of conventional store bought cigarettes and matched on the participants' menthol flavor preference (menthol vs. non-menthol) for 2 weeks to get acclimated to smoking research cigarettes. Participants who complete this 2 week period of smoking research cigarettes and want to continue with the study will enter the Randomized Double-Blind Phase.
3. During Randomized Double-Blind Phase 3, participants will be randomized (blinded) to either:
   a. continue to smoke the usual nicotine content (UNC) cigarettes from Phase 2 for the next 18 weeks
   b. switch to progressively reduced nicotine content (RNC) cigarettes over the next 18 weeks

   Tables 1 and 2 (see above) describe the dosing schedule for those randomized in the Phase 3.

4. Finally, during Treatment Choice Phase 4, both groups will then be offered the choice to:
   a. return to their usual brand (at their own cost)

b. Receive assistance to quit smoking (with counseling and FDA-approved medication provided at no cost for 11 weeks).

7.4.3. Method for Assigning Subject to Treatment Groups

Participants will be randomized to one of two experimental conditions based on a pre-determined random number sequence generated by Biostatistics core. Randomization will be stratified by site (Penn State and George Washington University) and by menthol flavor (regular/menthol). This ensures a similar distribution of treatment assignment (1:1 for gradual reduction: control) across study sites to avoid potential confounding.

7.4.4. Subject Compliance Monitoring

Compliance will be monitored throughout the trial by a) daily diary records; b) product accountability logs where the amount of product dispensed will be recorded and unused products collected and recorded; and c) questionnaires administered and clinic visits and during phone calls regarding the use of other tobacco or nicotine products. Participant's confidence in complying with the study protocols will be assessed at each study visit. Any problems that arise or they foresee happening will be discussed and problem-solved with the coordinator.

7.4.5. Blinding of the Test Article

Each carton is labeled with Research Triangle Institute (RTI) barcodes, log numbers, and batch/lot numbers. A packaging slip identifies the nicotine content. An unblinded cigarette administrator will remove all RTI identifiers and replace them with our own blind code labels. The blind code labels will be unique to each carton. The cigarette management software application, developed by the Public Health Sciences Data Management team, will house the blind code number for that carton and its corresponding carton information from RTI.

7.4.6. Receiving, Storage, Dispensing and Return

1. Receipt of Test Article

Experimental cigarettes will be provided free of charge to the investigators via the NIDA Drug Supply Program (see Notice: NOT-DA-13-002). They will be shipped in boxes to Penn State Hershey from the RTI in North Carolina. 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. Each carton is labeled with RTI barcodes, RTI log numbers, and batch/lot numbers. Individual packs and cigarettes do not have labels.

2. Storage

Cigarettes will be stored in locked standard freezers at Penn State Hershey. Once they are shipped to GWU they will be stored at room temperature. Menthol and non-menthol cigarettes will be stored in separate freezers. The cigarettes will be housed in space utilized for the Investigational Drug Service pharmacy and only the unblinded cigarette administrator and their supervisor will have access to the cigarettes. A service provided by Penn State will monitor and record the temperature of the freezers/fridges.

3. Preparation and Dispensing

Once the cigarettes are received from RTI, they will be blinded as noted above by the cigarette administrator under the supervision of the Investigational Drug Service (IDS) at PSU/HMC. When a person is entered into the cigarette management software application they are randomized to either UNC or RNC cigarettes. The application will use the randomization table provided by the Biostatistics Core to assign participants to either the UNC or RNC group. The application will assign the appropriate carton blind code number to dispense based off of the appropriate nicotine content for that participant. This will allow for a double-blind of the research coordinator and participant. A back up report of the cartons available, blind code, and corresponding nicotine level will be emailed to the cigarette administrator after each randomization so that if the cigarette management application is down we can still manually allocate appropriate cigarettes to a participant. An additional set of blind code labels will be attached to the carton that will be used to place on each cigarette pack in the carton. The labels will include the carton blind code, visit number, and space for participant ID.

4. Return or Destruction of the Test Article

Any unused experimental cigarettes that are returned from the participant will be destroyed according to the general policy for drug disposal of the IDS. A log will be kept on any cigarettes that are destroyed. We will not ship unused experimental cigarettes back to the NIDA Drug Supply Program.

5. Prior and Concomitant Therapy

Concomitant medications will be collected regularly throughout the trial to monitor participant health conditions.
Participants taking smoking cessation medication including bupropion in the prior 3 months will be excluded from the study. Medications related to certain medical conditions that are exclusions to the study, such as COPD and current heart conditions, will serve to alert the study staff of the presence of these conditions during screening. Once the participant is entered into the randomized double blind phase of the study, there are no medications that will interfere with the participant's ability to participate.

8. Data and Specimen Banking

8.1. Data and/or specimens being stored

Participants will be given an option on the consent form that will provide permission for the researchers to bank their biospecimens for future undetermined research projects. Only participants who consent to this option will have their blood, urine, and saliva specimens banked. Specimens will be stored with an ID code attached. The ID code will be associated with their data retained in REDCap. Data retained in REDCap will be stored indefinitely and may be used for future research. The research lab will be using software called Freezerworks to manage the biospecimens.

8.2. Location of storage

Specimens will be stored in the locked research laboratory of Dr. Muscat on the 3rd floor of the Cancer Institute. All data will be stored in REDCap.

8.3. Duration of storage

Participants that agreed to have their biospecimens banked will be stored indefinitely. REDCap data, data stored in Freezerworks, and any paper records will be stored indefinitely.

8.4. Access to data and/or specimens

The lab manager/technicians, study coordinators, and PI will have access to the freezer room where the specimens will be stored. The lab manager, research assistants, project managers, statisticians, and the PI will have access to the stored data in REDCap.

8.5. Procedures to release data or specimens

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

8.6. Process for returning results

Investigators will be required to provide a written report on their study results to the TCORS steering committee.

9. Statistical Plan

9.1. Sample size determination

The primary sample size calculation for this project will be based on hypothesis 1a and the main outcome variable is plasma cotinine concentration (measured as ng/ml). The mean value of this continuous varible will be compared between the control group and the experimental group. For plausible effect size and variation, we use results of Benowitz et al [4], where the mean (SD) of plasma cotinine concentration are 240 (120) for the control group and 113 (116) for the experimental group at the 21st week follow-up visit (end of randomization phase for trial). It is expected that the cotinine level in the experimental group is reduced gradually after the randomization and the mean difference of the cotinine level between these two groups at the beginning of the trial for our study will be smaller than the value of 127 ng/ml in Benowitz et al [4]. With a sample size of 70 participants per group, we are able to detect the difference in plasma cotinine concentration level between the two groups as small as 58 ng/ml with at least 80% power (and 68 ng/ml with at least 90% power). In this project we plan to study the mean change of plasma cotinine concentration separately for black and white populations. A total sample size of 280 (70 per group * 2 groups * 2 races) is then needed for this project. We plan to recruit a total of 400 participants for this project by allowing a 30% drop-out rate. The alpha level used for the power analysis is 0.05. Another biomarker of interest is the Glutathione (GSH, measured in μmol/ml). Within each study population (black or white), a sample size of 70 per

group will enable us to detect a mean difference of GSH of 0.23 with at least 90% power. The common standard deviation is assumed to be 0.40 based on Muscat et al (2004). For testing the menthol-by-group interaction effects, our proposed sample size will give us at least 80% power to detect a mean difference of plasma cotinine concentration of 72 ng/ml in the pair-wise comparison of among the group-by-menthol combination (4 levels, alpha is adjusted to 0.0083 by Bonferronni method).

9.2. Statistical methods

Basic baseline statistics including means (SDs) and frequency distributions (percentages) will be reported for demographic characteristics, subjective and objective measures (such as smoking history, the number of cigarettes and other nicotine products, and smoking topography measures). Where necessary, some characteristics will be reported by the two groups under investigation. Numerical baseline characteristics will be compared between the two groups using two-sample T-test or nonparametric Wilcoxon Rank-Sum test when appropriate. Suitably transformed variables will be used when necessary. Categorical variables will be compared using chi-square tests or Fisher's exact tests. Separate baseline analysis will be done within black and white samples in this study.

To determine the effect of progressive nicotine content reduction (NCR) on cotinine and other biomarkers of smoking exposure in both black and white smokers of lower SES over the 18 week trial period: for each of the biomarkers and other outcome variables of interest, exploratory data analysis will be conducted within each time period and across. Results will be summarized by table and figures (such as boxplots). Profile plots will be generated to show the trajectory of variable across different time periods. The major analytical tool for addressing the specific aims of this study is linear mixed models with repeated measures. For each biomarker and other numerical outcome measures of interest, a linear mixed model for repeated measures will be fit to evaluate the main effects of time, group, and time-by-group interaction; treating baseline scores for outcomes as covariates. Known confounders will be included in the linear models, and other covariates will be included if their individual bivariate associations with both the group variable and outcome are significant at 10% level. The magnitude and direction of the difference between the treatment groups will be quantified by reporting the estimated least-square mean differences at each time point. Separate analysis will be performed in black and white samples individually. We will also test for a number of potential effect modifiers by pooling the trial data of white smokers and black smokers together. Interaction terms that do not reach statistical significance will be dropped from the final model.

To determine the modifying effect of menthol on progressive nicotine content reduction and biomarkers: modification effects such as the menthol will be examined by incorporating the menthol-by-group interaction in the multi-variable linear mixed model. The three-way interaction of the menthol-by-group-by-time will be explored but will be removed from the model if not significant. If the menthol-by-group interaction were found significant then mean-profile plot will be used to show the interaction in details.

To determine the predictors of participant drop-out/relapse: it is hypothesized that compensatory smoking behavior as measured by smoking topography and expired carbon monoxide, a higher baseline nicotine dependence behavioral score and rapid nicotine metabolism phenotypes will be associated with drop-out/relapse. The status of drop-out/relapse will be combined with the length of time from randomization to drop-out/relapse or loss of follow-up to form a time-to-event type of variable. Participants who completed the randomization phase of study will be considered as censored records. Kaplan-Meier type analysis (for categorical predictors) or simple Cox proportional hazard regression model (for quantitative predictors) will be used to examine the bivariate associations between the possible predictors and time to drop-out. If a predictor has shown marginal significance (with p-value less than 0.10) in the bivariate analysis then it will be kept in the multiple regression analysis. A multi-variable Cox proportional hazard regression

model will be built to examine the effects of the predictors jointly for time to drop-out. The magnitude and direction of effectiveness will be quantified by the estimated hazard ratios with their 95% confidence intervals. The interaction between the predictors will be explored in the analysis but will be removed if not significant.

To determine if a gradual reduction in reduced nicotine content cigarettes vs. same nicotine content is associated with a reduction in stress: the stress level is measured by both salivary biomarkers and psychological variable. Cortisol values measured at different time of a day will be summarized to peak daily cortisol and cortisol drop variables. Summary statistics will be generated to describe the trend of cortisol variables over visit by group. T-tests or nonparametric Wilcoxon Rank-sum test will be used to compare salivary cortisol measures between the two study groups at each time point. Similar to previously described, linear mixed model for repeated measures will be fit to evaluate the main effects of time, group, and time-by-group interaction; treating baseline cortisol scores as a covariate. The psychological variables for stress levels will be analyzed in a similar statistical fashion.

10. Confidentiality, Privacy and Data Management

10.1. Confidentiality

The majority of study data at both sites will be collected and 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. REDCap is HIPAA compliant. Data are stored on a secure server at Hershey Medical Center and data in REDCap are encrypted. Access to the database requires authentication (a unique username and password) and a user matrix will be used to ensure that only appropriate data are accessed based on the individual's role on the project. Every interaction with the data is logged in REDCap creating an audit trail.

Paper files will be kept to a minimum and those that are generated will be stored in locked filing cabinets in the research offices of Dr. Joshua Muscat. Electronic data stored outside of REDCap (i.e. smoking topography data) will be stored on password protected computers and password protected file share directories.

10.1.1. Identifiers associated with data and/or specimens

The following personal identifiers will be collected:

- Name
- Address
- Phone numbers
- Email addresses
- Date of birth
- Code number

1. Use of Codes, Master List

Majority of study data will be collected in REDCap including a participant record number and a study specific code number. The list connecting the participant data to the code numbers will be stored electronically in REDCap and will not be destroyed. The PIs, Study Coordinators, Research assistants and Lab Managers will have access to the list.

10.1.2. Storage of Data and/or Specimens

- **Electronic data** will be stored indefinitely in REDCap with identifiers attached. Smoking topography data will be stored electronically on password protected computers and password protected file share directories managed by Public Health Sciences (PHS) IT department.
- **Paper records:**
  - Paper will be stored with ID code number and/or participant name attached indefinitely in locked filing cabinets in the research offices of Dr. Muscat. Paper records will be scanned and uploaded into participant records in REDCap. Electronic copies will be stored indefinitely as above.
- **Specimens:**
  - Prior to processing, samples will be placed in a refrigerator by the research assistant or study coordinator in the key-card secured lab of Dr. Josh Muscat.
  - Within 24 hours, samples will be processed by a lab manager and will then be secured in a freezer located in the locked research laboratory of Dr. Josh Muscat on the 3rd floor of the Cancer Institute.
  - Specimens will be stored with a code number attached.
  - To manage the specimens within the freezer the lab manager will be using software called Freezerworks which will be housed on the PHS password secured file share directory on the PHS secure network. The code number, visit number, date/time of collection, processing and storage, and consent options for future use of samples will be stored here in addition to REDCap.

10.1.3. Access to Data and/or Specimens

Electronic data: PI's, Study Coordinators, Research Assistants, and lab manager will have access to the REDCap data and password protected file share directories. However, a REDCap user matrix will limit access to data based on the researcher's role in the study.

Paper records: PI's, Study Coordinators, and Research Assistants will have access to the paper records.

Specimens: Only the study coordinators, lab manager/technicians, and PIs will have access to the specimens and Freezerworks once they have been processed and secured in the freezer room.

10.1.4. Transferring Data and/or Specimens

Processed, frozen specimens from the George Washington University study site will be shipped via commercial carrier or driven to Dr. Muscat's Penn State laboratory for storage and eventual analysis. Only ID code numbers will be attached to these specimens.

10.2. Privacy

The research team will only have access to data that they have consented to provide and is provided by the participant during data collection contacts. HIPPA guidelines will be followed for all participants. Participants will be informed that they can refuse to answer any questions that make them feel uncomfortable. The majority of personal data that the participants provide

will be entered directly into REDCap by the participant. All study visits, data collection and procedures will be completed in private consult rooms at the Penn State Hershey CTSI.

11. Data and Safety Monitoring Plan

11.1. Periodic evaluation of data

The Biostatistics Core will prepare a cumulative report of all data points listed below for the Safety Monitor to review every 6 months after recruitment begins. The report will include site information.

11.2. Data that are reviewed

Data that will be reviewed include:

- Baseline sociodemographic characteristics
- Accrual and retention
- Adverse and serious adverse events
- Protocol deviations/violations
- Changes in conflicts of interest
- Patients' ability to achieve study requirements (compliance)
- Changes in cigarette consumption from baseline
- Exhaled carbon monoxide increase from baseline

Other information:

- Copy of Current IRB approved protocol
- Copy of Current IRB approved Consent Form
- Most recently submitted IRB Continuing Review

11.3. Method of collection of safety information

All safety data will be directly coded into REDCap during study visits across both sites and will be accessible at all times to the sponsor site. Every study visit participants will be asked a series of standard questions that would trigger an assessment for an adverse event to be documented. An adverse event will also be documented if a participant volunteers information about changes in their health either at study visits or on phone call interviews. 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.

11.4. Frequency of data collection

Adverse events will be collected at every visit and also may be collected when the participant volunteers information between visits (e.g. phone call interviews). Carbon monoxide levels will be collected at every clinic visit. Cigarettes smoked per day will be collected at every clinic visit and during phone call interviews. Compliance will be monitored throughout the trial by a) daily diary records; b) product accountability logs where the amount of product dispensed will be recorded and unused products collected and recorded; and c) questionnaires administered and clinic visits and during phone calls regarding the use of other tobacco or nicotine products. Cumulative data will be gathered every 6 months for review by the Study Monitor.

11.5. Individual's reviewing the data

Rebecca Bascom, M.D., M.P.H (Professor of Medicine, Expertise: Pulmonary Medicine) will be the Study Monitor and will be responsible for reviewing the DSM report. The research coordinator will be responsible for the daily oversight of the study and recording safety data. The PI and, if needed, the Study Monitor will review all adverse events.

11.6. Frequency of review of cumulative data

Cumulative data will be reviewed every 6 months after recruitment begins. The study monitor 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 difference between groups or unacceptable adverse events. A copy of the Study Monitor's review of the DSM report will be shared will the PI, Penn State IRB, NIH, and any other appropriate regulatory bodies.

11.7. Statistical tests

Basic descriptive statistical methods will be used to analyze the safety data to determine whether harms are occurring. Changes in cigarette consumption from the baseline will be calculated. The exhaled carbon monoxide increase from baseline will be examined in the same way. 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.

11.8. 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 study monitor identify any issues after reviewing the cumulative data, these recommendations will be followed.

12. Risks

Potential risks for subjects are minimal. The cigarettes which will be administered to subjects have been previously tested and found to be of no greater risk than cigarettes the participants are already using. Subjects will be under supervision throughout their participation in the study and adverse symptoms will be recorded at each in person clinic visit and monitored by the study coordinators. The major side effects associated with RNC cigarettes are similar to usual brand cigarettes.

Additional potential risks include:

- **Increased compensatory smoking:** Compensatory smoking may lead to 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.
- **Nicotine withdrawal symptoms:** Decreased nicotine cigarettes may result in nicotine withdrawal symptoms (e.g. irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, insomnia/sleep problems, impatience, headache, difficulty concentrating). These symptoms will be monitored regularly.
- **New development of pregnant or want to become pregnant:** Smoking is known to be harmful to the developing human fetus. For this reason women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the standard duration of the study.
- **Risks of standard venipuncture:** The discomfort associated with removing blood by venipuncture (by needle from a vein) is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

- **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:** You will be assigned to a study treatment by chance. The treatment you receive may prove to have more side effects than the other study treatment.
- **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.
- **Use of oral nicotine replacement:** During the Treatment Choice Phase of the study, participants will be encouraged to quit smoking and will be offered an 11 week supply of oral nicotine replacement therapy (NRT) (lozenge or gum). NRT (lozenge or gum) are known to be safe and have only mild side effects. For this reason they are generally sold over the counter. Excess nicotine can cause mild symptoms such as nausea, dizziness, diarrhea and rapid heartbeat. Occasionally these (or other rarely occurring symptoms) are more severe. There is a slight risk that subjects who have progressed to very low nicotine cigarettes and then choose treatment with the NRT will obtain more nicotine than they are used to. A 24 hour period of cigarette and NRT abstinence will be recommended to the participants who want to quit. Participants will be seen after this waiting period and their craving and withdrawal will be assessed. Those who have very low or no withdrawal or craving will be offered the lowest dose and frequency of NRT. They may also choose to not use any NRT during their quit attempt. Those who elect to use NRT will be contacted weekly to monitor their tolerance.

  The use of oral nicotine replacement allows the participant to self-monitor their urges and cravings and use only the amount of NRT that they feel is necessary. A protocol to help the researcher determine the best dose of NRT to recommend to the participant will be used. Participants will be followed up within 48 hours of starting NRT to assess tolerance.

13. Potential Benefits to Subjects and Others

13.1. Potential Benefits to Subjects.

There is no guaranteed direct benefit to the individuals participating in the research study. There is a possibility, although uncertain, that participation in this study may reduce their nicotine dependence. Subjects will receive cessation aid if they choose to quit in the treatment choice phase of the study.

13.2. Potential Benefits to Others

Society as a whole will benefit from the research because it is expected to provide important information on the effectiveness of smoking reduction strategies.
Cigarette smoke is the leading preventable cause of disease and current evidence-based interventions are ineffective for many current smokers. The study should help uncover whether alternative low nicotine tobacco products reduce dependence.

14. Sharing Results with Subjects

Pregnancy tests will be given to female participants at the initial screening visit. If the test is positive the results will be shared with the participant and they will be advised to follow up with their doctor and that they will not be allowed to participate in the study. Blood pressure that is high will be told to the participant at their in person visits. No results will be shared with others, such as the participant's primary care physician. Upon participant completion of all study related procedures, participants will be sent a letter in the mail telling them which cigarette group they were randomized to in the study. Within the letter the link to the clinicaltrials.gov with the study

registration number will be included so that they can look up the study results. The letter is uploaded in CATS under Supporting Documents named 'Randomization Assignment letter'.

15. Economic Burden to Subjects

15.1. Costs

The only cost associated with participation in the research is travel to and from the clinic on clinic visit days. They will be reimbursed with a gift card to cover costs of transportation.

15.2. Compensation for research-related injury

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

16. Number of Subjects

The project will recruit a total of 400 participants. We will recruit 200 participants at Penn State Hershey, allowing for a 30% withdraw rate and 280 subjects needed to complete the entire protocol.

17. Resources Available

17.1. Facilities and locations

Passive recruitment will takes place with flyers and handouts at locations where smokers frequent, i.e. gas stations, grocery stores, and on area community boards. Study procedures will take place in one of the private clinic rooms in the Clinical Research Center at Penn State Hershey.

17.2. Feasibility of recruiting the required number of subjects

Recruitment is open to all lower socioeconomic smokers where prevalence of smokers is greater than higher socioeconomic groups (35.8%, low SES vs. 15.7%, high SES). We also have a list of 300 potential smokers from our recent study of "Socioeconomic Status and Smoke Exposure in Appalachia" (IRB #37860) who have consented to be contacted for research studies. In addition, favorable word of mouth from smoking participants to their family/friends/coworkers has served as a significant source of recruitment in past research studies. So feasibility of acquiring participants is good.

17.3. PI Time devoted to conducting the research

PI has committed 25% FTE in years 1-5 for the project.

17.4. Availability of medical or psychological resources

It is not anticipated that participants will need any medical or psychological resources as a result of being in this study. Safety of the participants will be monitored throughout the study.

17.5. Process for informing Study Team

All members of the study team and across sites will have completed all necessary training and documentation will be collected. The study coordinator will train personnel on additional protocol procedures and this will be documented. The project will also have a shared workspace to upload site specific documentation, for example, training documents, SOPs, IRB documents, and current protocols.

18. Other Approvals

Dr. Muscat's lab is approved under the Institutional Biosafety Committee- JEM14-01-2 for work with human body fluids (documentation is uploaded under Supporting Documents). We received an Investigational Tobacco Product application approval from the Center for Tobacco Products for use of the research cigarettes. We obtained a Certificate of Confidentiality. We received approval by the CRC Advisory Committee. All of these will be uploaded to the Supporting Documents section.

19. Subject Stipend and/or Travel Reimbursements

Subjects will receive a $20 gift card per clinic visit to cover parking, meals, and travel for the 11 clinic visits ($220). Subjects will receive $20 for the initial screening visit and the last study visit will receive $60 for completing each of the remaining 9 clinic visits ($580) after enrollment. Subjects will receive $10 for each of the 7 phone surveys they complete ($70). If subjects complete all clinic visits and return used and unused cigarette packs and study equipment (e.g. smoking topography device) they will receive a $130 study compliance payment. Total payment would be $1000.

The P will receive a $130 compliance payment included in their last visit payment if:

a. Participants complete all study visits they will receive $65

b. Return all study supplies (i.e. smoking topography device and study cigarette packs (unopened, opened, and empty)) within a margin of 4 packs for 5/7 study visits where research cigarette return was required (visit 3, 4, 5, 6, 7, 8, and 9) they will receive $65.

If subjects are asked to continue using the smoking device throughout the study they will receive an additional one-time check payment of $60 for completing this extra protocol. If they were asked to provide saliva samples throughout the study they will receive an additional one-time check payment of $35 for completing this protocol. If the participant does not complete the protocol, they will not receive payment.

Payment Schedule:

Study Visit/Contact	Transportation	Visit/Survey Payment	Compliance Payment	Total
Orientation/ Assessment Visit 1	$20	$20		$40
Clinic/Bio Visits 2-10	$20	$60		$80
Phone Survey		$10		$10
Final Visit 11	$20	$20	$130	$170

20. Multi-Site Research

20.1. Communication Plans

Both sites (Penn State Hershey and George Washington University) will agree on a standing telephone conference call at least monthly to discuss any problems with accrual, participants, data collection, or procedures. During these calls, the number of Ps enrolled, P compliance, results from data monitoring, and other issues of concern will be discussed. More immediate situations will be brought to the PI's and study staff who will discuss further actions. The project will have a shared workspace to ensure all sites have the most current versions of IRB documents, procedures, and approvals. Modifications will also be uploaded here and communicated to the sites. For the sponsor site, this will also serve as a place to ensure all approvals are obtained from the other site.

20.2. Data Submission and Security Plan

The majority of study data will be directly coded into a secure REDCap database either by the research staff or the participant at the clinic visit. The REDCap database is hosted within the Penn State College of Medicine and will be used as a central location for data submission for both sites. Sites will only have access to their own data by using Data Access Groups in REDCap. As a result, data security is embedded in the data collection plan. Paper copies of written consent will be scanned and uploaded into the participant record in REDCap. Site audits will be conducted to ensure that paper data is secure. Electronic data quality checks through REDCap will be conducted by the Penn State site to ensure that electronic data is being entered correctly.

20.3. Subject Enrollment

Screening and enrollment data will be directly coded into REDCap and they will be assigned a study ID. The PI and study coordinator will have access to screening and enrollment data across sites to ensure both sites are enrolling as anticipated. Participants will be randomized to one of two experimental conditions based on a pre-determined random number sequence generated by the Penn State Biostatistics and Database Management Core and will be housed within the cigarette management software application. The cigarette management software application is web-based and will be accessible to the George Washington site.

20.4. Reporting of Adverse Events and New Information

All Adverse Event information will be coded directly into REDCap at each clinic visit and will be monitored at each study site by Drs. Muscat and Horn. The respective PI's and study personnel will be responsible for the reporting of AEs and new information as required to their IRB and other agencies. Discussion of AEs and new information will be conversed at least monthly during the telephone conference calls across sites. All serious adverse events that occur at either site (regardless of causality) will be submitted to the FDA within 5 business days.

20.5. Audit and Monitoring Plans

The study team meet will at least monthly over the phone to discuss any issues that might arise with participants, screening, enrollment, participant adherence to the study protocol, or problems with implementing the protocol at each site. Data will be monitored through electronic data checks that will be executed in REDCap. The Penn State TCORS Biostatistics team will perform monthly data quality checks to monitor missing or invalid data.

21. Adverse Event Reporting

21.1. 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.

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21.2. Recording of Adverse Events

The occurrence and recording of adverse events will be sought by asking a series of standard questions to the participant at each visit during the study. Adverse events also may be detected when the participant volunteers them during or between visits or through clinical assessments (e.g. exhaled CO).

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.

21.3. Causality and Severity Assessments

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

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as *associated with the use of the study cigarettes* 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.

21.4. Reporting of Adverse Reactions and Unanticipated Problems to the FDA

21.4.1. Written IND Safety Reports

N/A

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

N/A

21.5. 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) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.6. Unblinding Procedures

If an adverse event requires the subject to be unblinded, the unblinded study personnel (cigarette administrator) will be able to provide that information as needed. Otherwise, participants will not be unblinded to their cigarette allocation.

21.7. Stopping Rules

No formal *a priori* statistical stopping rules will be used for interim monitoring of the primary or secondary endpoints given the risk involved in the study. Analyses will be performed and comprise of endpoints associated with safety and study integrity i.e. recruitment rate, completion rate, rates of SAEs/AEs (including changes in cigarette consumption/exhaled carbon monoxide from baseline), and any other variables that are requested from the study monitor. An unblinded bi-annual summary report of these analyses will be prepared by the Biostatistics Core for the study monitor to review. The study monitor 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.

22. Study Monitoring, Auditing and Inspecting

22.1. Study Monitoring Plan

22.1.1. Quality Assurance and Quality Control

Overall responsibility for data quality and study conduct lies with the PIs of the project. The daily oversight of the adherence to the study protocol and collection of participant's data will be conducted by the research coordinator and overseen by the PI. Site visits will be conducted by the Penn State University research team before and during enrollment to ensure that proper equipment and facilitates are set in place and procedures are being executed in compliance with the protocol and IRB policies. Checklists will be provided across sites of all the measures that need to be collected and the order of administration. Any issues that arise with the study procedures and progress will be addressed to the PI and across sites during regular conference calls.

Random data entry checks across sites will be implemented by the research study team to identify problems with data entry. Data quality tools included in REDCap will be utilized by the research coordinator to identify incorrect data types, out of range data, and missing data across sites. 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. Any problems detected after the participant has left will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

22.1.2. Safety Monitoring

The PI and co-PI of the project will be responsible for monitoring the overall safety and integrity of the research project with the help of the study coordinators. Every 3 weeks participants will be seen by the coordinators who will assess adverse events throughout the study using the Adverse Events Trigger Questions (uploaded in Supporting Documents). If there are any concerns on participant safety they will be brought to the PI. Participants will be seen by a research nurse while at the PSH Clinical Research Center. Dr. Muscat will meet weekly with the study staff to review participant's progress and their experiences with the tobacco products, including any adverse events.

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE log by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the Penn State IRB, NIH, FDA, and the Safety Monitor of all applicable AEs as appropriate.

The **research coordinator** will complete the appropriate report form and logs at study visits; assist the PI to prepare reports and notify the Penn State IRB, NIH, FDA, and the Safety Monitor of all applicable AEs as appropriate.

The **Safety Monitor** will assess AEs and confirm that they are correctly entered into the events log; confirm that the AEs are reported to the appropriate regulatory bodies, as required; review the DSM report and provide a written summary for the study record, Penn State IRB, and other regulatory agencies.

Similar procedures will be instituted at George Washington University under the supervision of Dr. Horn. Any adverse symptoms will be discussed over the telephone on the biweekly calls across the sites and with the Study Monitor, as needed. Urgent issues can be dealt with more immediately.

22.2. Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

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