The Role of Nicotine Dose and Route of Delivery in Affecting Adoption of E-cigarettes and Reducing Exposure to Toxic Combustion Products

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PURPOSE OF THE STUDY:

We propose to assess the relative role of nicotine dose and route of delivery in affecting successful switching from combustible cigarettes to e-cigarettes, as well as concomitant reductions in *ad libitum* cigarette smoking and exposure to harmful and potentially harmful constituents of combustion.

The strategy will be to assess adoption of e-cigarette use and concomitant reduction in *ad libitum* smoking of subjects' usual brands of cigarettes over an 8-week period, during which they will receive nicotine or non-nicotine e-cigarettes, and nicotine or non-nicotine skin patches. The nicotine patches will not be used as a therapeutic treatment in this study, but rather as a way to manipulate the nicotine dose, while varying the rate and route of nicotine delivery. Behavioral or "habit" aspects of e-cigarette use will be controlled for by the groups receiving non-nicotine e-cigarettes.

BACKGROUND & SIGNIFICANCE:

Cigarette smoking remains the leading cause of preventable disease and death in developed countries, due principally to its contributions to heart disease, chronic obstructive pulmonary disease (COPD), and cancer (Lando & Wilson, 2010). The annual death toll in the U.S. from diseases caused by smoking has been increasing steadily and is estimated to be the highest ever, 540,000/year (Carter et al., 2015).

The U.S. Surgeon General's Report of 2010 (USDHHS, 2010) concluded that the combustion products of smoke, rather than nicotine, were responsible for most smoking related diseases. E-cigarettes, which deliver nicotine in the absence of combustion, have been advanced as a tobacco harm reduction strategy. Thus far, however, only a minority of smokers have adopted e-cigarettes to satisfy their nicotine dependency without concurrent use of combustible cigarettes. A number of factors may serve as barriers to the adoption of e-cigarettes, including insufficient dose of nicotine and lack of familiar sensory/habit components (e.g., aroma, "throat hit") associated with smokers' usual brands of cigarettes. The present study will examine the relative roles of nicotine dose and route of administration in affecting the ability of smokers to transfer their dependency from combustible cigarettes (CC) to e-cigarettes.

There are several reasons why administration of a given dose of nicotine by inhalation (via e-cigarettes), vs. transdermal administration (via nicotine patches) would be more reinforcing and lead to greater switching from combustible cigarettes to e-cigarettes. First, inhaled nicotine reaches the bloodstream and brain much faster than transdermal administration (Rose et al., 2010), producing immediate reinforcing effects. Also, inhaled nicotine produces familiar respiratory tract cues that smokers find rewarding (Rose, 2006). Indeed studies have reported a greater suppression of combustible cigarette use when smokers used e-cigarettes as an alternative compared with nicotine patch (McRobbie et al., 2014).

Although subjects receiving nicotine from e-cigarettes will no doubt receive a range of nicotine doses, depending on the extent of use, data from previous studies (Shahab et al., 2017) suggests that the mean dose is expected on average to be similar to that provided by a 21 mg/day patch (and actual mg/day, as estimated from the number of e-liquid cartridges consumed, will be a covariate in the statistical analyses described below).

DESIGN & PROCEDURE:

Design Overview

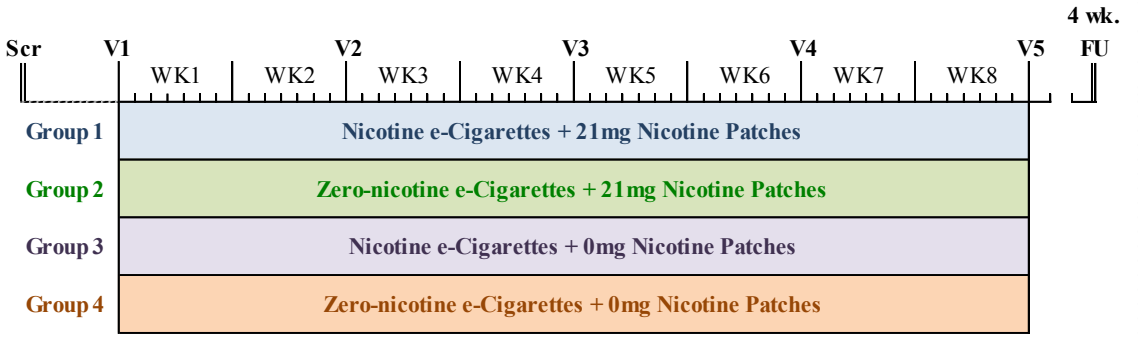
The study will comprise a randomized, double-blind parallel-arm study to ascertain the role of nicotine dose and route of administration in reducing use of combustible cigarettes and in facilitating adoption of e-cigarettes. Two hundred sixty daily cigarette smokers will be randomly assigned to receive 8 weeks of exposure to the following conditions (65/group):

1. Nicotine containing e-cigarettes + 21 mg nicotine skin patches
2. Zero-nicotine e-cigarettes + 21 mg nicotine skin patches
3. Nicotine containing e-cigarettes + 0 mg skin patches
4. Zero-nicotine e-cigarettes + 0 mg skin patch patches

Nicotine and non-nicotine e-cigarettes will be purchased from JUUL Labs. The JUUL is a rectangular closed-system e-cigarette. This e-cigarette was commercially available as of August 8, 2016 and does not contain any alterations to the chemistry or physical characteristics. Each JUUL Pod pack contains 4 pods. Each JUUL Pod contains 0.7mL with 5% nicotine by weight, approximately equivalent to one pack of cigarettes or 200 puffs. Multiple flavors will be used in this study in order to more accurately mimic real world conditions. Each pack contains four of either tobacco-flavored or mint-flavored pods. Subjects will be provided with enough additional packs of pods to use during the smoking period. JUUL Pods are sealed system cartridges for use in the JUUL e-cigarette. Each pod is contained in tamper resistant blister packs. The nicotine patches will be purchased from Duke Outpatient Pharmacy and non-nicotine patches will be obtained from Rejuvenation Laboratories.

Ad libitum smoking will be assessed weekly using daily diary recordings of cigarettes smoked per day as well as the objective index of expired air carbon monoxide (CO) levels measured at the study visits.

The Study timeline is shown below:



Screening and Session Procedures

Interested potential subjects will respond to advertisements by contacting our Center to be phone screened. Potential subjects will be given a brief description of the study and will be asked questions to assess eligibility and interest. Eligible subjects interested in participating will be scheduled for the medical history and physical examination screening visit.

After granting their informed consent, potential subjects will be given the HIPAA Notice of Privacy Practices. They will also complete a medical history form and will have their blood pressure, pulse, weight, height, temperature and expired air CO measured. Subjects will provide smoking history information, a saliva sample, blood (maximum of 50mL) for tests to measure general health, nicotine metabolite ratio (NMR), and for genetic evaluation, and urine for urinalysis and illicit drug testing. Women of child bearing potential will also have a serum pregnancy test. The study physician or one of his assistants will perform a physical examination and an ECG. The ECG will be used to screen for the presence of major arrhythmias such as atrial fibrillation, SVT, and bradycardia. It will also be used to confirm positive physical exam findings.The screening visit will last approximately 2.5 hours.

Blood and urine specimens will be sent to LabCorp for processing. The results of laboratory blood and urine tests will not routinely be given to participants to send or be sent to their physician to include in their medical record. However, if the subject's lab results are outside the acceptable range for participation in the study the Physician/P.A. will send the subject a medical exclusion letter and a copy of the lab results. Participants who are accepted into the study but need medical follow up due to minor abnormalities in lab results will also be informed by letter from the Physician/P.A. A copy of the laboratory results will be included with the letter, which will also indicate that the condition does not interfere with his/her participation in the study.

The blood samples for genetic evaluation and NMR will be stored at the Center for Smoking Cessation. If they are sent to an external lab for analysis (to be determined), there will be no identifiers except for a code number on the samples.

The time commitment for subjects is 8 weeks once their participation begins, plus one follow-up session at four weeks. Subjects will return every two weeks to obtain e-cigarette and patch supplies, and for outcome measures of e-cigarette and combustible cigarette use to be collected.

Questionnaires will be completed within REDCap on a desktop computer in the Center office. The technician will log on to the REDCap site and will open the questionnaires for the subjects. Subjects will only have access to their questionnaires. Access to any other websites will be blocked by Duke Psychiatry Information Technology.

Sessions

The first study visit (V1) will take place approximately one week after the screening visit. Subjects will complete baseline questionnaires and will be randomized to one of the four groups. Subjects will be tested for exhaled air carbon monoxide, and saliva samples will be collected for analysis of smoking related chemicals (e.g., cotinine). They will also have their blood pressure, heart rate and weight measured. Subjects will also complete questionnaires assessing their dependence on cigarettes (Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991)), and rewarding effects of cigarettes (modified Cigarette Evaluation Questionnaire (Cappelleri et al., 2007)).

Subsequent study visits will occur approximately two weeks apart (with a five-day window on either side of the scheduled visit). Subjects will complete questionnaires and be tested for exhaled air carbon monoxide, provide a saliva sample for analysis of smoking related chemicals (e.g., cotinine), and have their blood pressure, heart rate and weight measured. Subjects will also complete questionnaires assessing their dependence on cigarettes (Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991)), and rewarding effects of cigarettes (modified Cigarette Evaluation Questionnaire (Cappelleri et al., 2007)).

At the first (V1) and final (V5) sessions, we will assess total urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The half-life of NNAL is 10 days (Goniewicz et al., 2009), yielding a valuable index of sustained reductions in cigarette smoking, The half-life of expired air CO, in contrast, is 4.5 h (Sandberg et al., 2011). Also at these two visits subjects will use one of the e-cigarettes for ten minutes. By weighing the device before and after puffing, an estimate of mouth nicotine intake or placebo aerosol intake will be obtained. Subjects will refrain from smoking for one hour prior to using the e-cigarette.

Subjects will also be given diaries to record the number of cigarettes smoked each day and e-cigarette cartridges used, and will be instructed to return the diaries at the next visit. At Sessions V1-V4, participants will be dispensed a sufficient supply of skin patches and e-cigarette refill tanks (pods) to last until the next session. Participants will be given pods with both flavors (Virginia tobacco and cool mint) of e-liquid. They will be

asked to return all used and unused pods and used patches at their subsequent visit for proper disposal and compliance monitoring.

Four-week Follow-up

Study participants will return to the laboratory for a brief follow-up session four weeks after Session V5. This session will include an expired air CO reading, blood pressure, heart rate and weight measurements, collection of saliva and urine samples, and completion of several questionnaires.

SUBJECT IDENTIFICATION:

We propose to enroll up to 1600 smokers in order to identify 260 participants who meet all criteria to be accepted into the study and to be randomized into one of four experimental conditions.

Inclusion Criteria

- Are 18-65 years old;
- Smoke an average of at least 10 cigarettes per day;
- Have smoked at least one cumulative year;
- Have an expired air CO reading of at least 10ppm;
- Have a body weight of $\geq$ 110 lbs. (50 kg) and $\leq$ 300 lbs. (136 kg);
- Are able to read and understand English.

Potential subjects of child bearing potential must agree to use two acceptable forms of contraception during their participation in this study. Women are considered past the age of child-bearing potential if:

- they are greater than 55 years of age, OR
- they are at least 50 years of age AND have not menstruated for at least
- 12 months, OR
- have a documented Follicule Stimulating Hormone (FSH) level of greater than
- 40 mIU/mL.
- they are at least 45 years of age AND have not menstruated for at least 18
- months, OR have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL.

Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Potential subjects must agree to avoid the following during their participation in this study:

- participation in any other nicotine-related study protocol outside of this protocol;
- use of tobacco products other than cigarettes, including pipe tobacco, cigars, e-cigarettes, snuff, and chewing tobacco;
- use of experimental (investigational) drugs or devices;
- use of illegal drugs;
- use of exclusionary medications.

Exclusion Criteria

- Hypertension – systolic BP > 160 mm Hg, diastolic BP > 100 mm Hg. Individuals with a history of hypertension may be allowed to participate in the study if the study physician or medical provider determines that the condition is stable and will not jeopardize the individual's safety.
- Hypotension (with symptoms) – systolic BP < 90 mm Hg, diastolic BP < 60 mm Hg.
- Coronary heart disease with symptoms (e.g., chest pain)
- Heart attack in the past year
- Cardiac rhythm disorder (irregular heart rhythm with symptoms)
- Chest pain in the last month (unless history indicates a non-cardiac source)
- Symptomatic heart disorder such as heart failure
- Advanced liver or kidney disease that requires medication or dialysis, paracentesis
- Major gastrointestinal illness (e.g. Celiac disease, Crohn's dx Ulcerative Colitis)
- Bleeding stomach ulcers in the past 30 days
- Lung disease that requires oxygen
- Major brain disorder (including stroke with residual deficit, brain tumor, and seizure disorder)
- Migraine headaches that occur more frequently than once per week
- Recent, unexplained fainting spells
- Problems giving blood samples
- Diabetes with insulin use or with HbA1C over 7%
- Current cancer or treatment for cancer in the past six months (except basal or squamous cell skin cancer)
- HIV, Hepatitis B, or Hepatitis C
- History of Tuberculosis or recent positive PPD
- Other major medical condition (as determined by study physician)
- Currently symptomatic psychiatric disease (as determined by study physician)
- Psychosis, bipolar disorder, or psychiatric hospitalization within the past 12 months
- Suicidal ideation (thinking about ways to commit suicide) (within the past 12 months) or a lifetime occurrence of attempted suicide;
- Current depression – The Patient Health Questionnaire PHQ-9 for Depression will be used to screen for current (within 2 weeks) depression. Potential subjects who score >9 (or who score >0 on item #9 ("Thoughts that you would be better off dead, or of

hurting yourself in some way") will be excluded from study participation, and, at the discretion of the study physician, referred to appropriate psychiatric treatment;

- Pregnant or nursing mothers
- Use (within the past 30 days) of:
  - Illegal drugs (or if the urine drug screen is positive for THC, Cocaine, Amphetamine, Opiates, Methamphetamines, PCP, Benzodiazepines, or Barbiturates), unless recent use of prescription Opiates or Benzodiazepines were taken for management of acute symptoms (e.g., tooth extraction, recent surgery);
  - Experimental (investigational) drugs;
  - Psychiatric medications including antidepressants (SSRIs, SNRIs, TCAs, MAOIs, St. John's Wort), lithium, anti-psychotics or any other medications that are known to affect smoking cessation (e.g. clonidine);
  - Phentermine, triptans, tryptophan, linezolid, dextromethorphan, opiates (unless taken for management of acute symptoms), tramadol, or dopamine agonists;
  - Any agents that have documented correlation with increased incidence of valvulopathy and/or pulmonary hypertension (e.g., cyproheptadine, trazodone, nefazodone, amoxapine, tricyclic antidepressants, mirtazapine, pergolide, ergotamine, methysergide) (or anticipated use during the study);
  - Wellbutrin, bupropion, Zyban, Chantix, varenicline, nicotine patch, nicotine replacement therapy or any other smoking cessation aid. Use of cigars, cigarillos, pipes, Hookah, dissolvable nicotine, snuff, chewing tobacco, or e-cigarettes within the past 30 days
- Concurrent use of a serotonergic agent/combination associated with severe serotonin syndrome (within the past 30 days)
- Use of cigars, cigarillos, pipes, Hookah, dissolvable nicotine, snuff, chewing tobacco, or e-cigarettes within the past 30 days
- Self-report of consuming more than 6 alcoholic drinks on 1 or more days per week
- Significant adverse reaction to nicotine patch in the past
- Current participation or recent participation (in the past 30 days) in another smoking study at our Center or another research facility
- Current participation in another research study

Assessment of Eligibility

Potential subjects who do not have a self-reported diagnosis of the above listed conditions may be excluded if the study physician or physician assistant determines that the history, physical findings, ECG, or laboratory studies reveal information that may jeopardize the subjects' safe study participation. For medical conditions that do not appear above, the study physician will be consulted, and if the medical condition does not jeopardize safe study participation, then the subject may be enrolled.

SUBJECT RECRUITMENT AND COMPENSATION

Subject Recruitment

Smokers with no major health problems will be recruited from communities in and around Durham, North Carolina. Recruitment will occur through newspaper, flyers, and internet advertisements and by word-of-mouth. Potential subjects will be pre-screened on the phone by a member of the Duke CSC. If potential subjects meet the pre-screening study requirements and are still interested in participation, they will attend a physical screening session at the Duke CSC, located at 2424 Erwin Road, Suite 201, Durham, NC 27705. If after this visit it is determined that they qualify for participation, they will attend subsequent study visits at the Duke Center for Smoking Cessation located at 2424 Erwin Road, Suite 201, Durham, NC 27705.

Subject Compensation

Subjects will be reimbursed $40 per visit for attending the five study visits, plus $60 for attending the follow-up visit. In addition, subjects will receive a payment of $10 for each of the 5 visits attended in which they return their completed take-home forms (brief questionnaires which describe subjective effects of product use and record smoking behavior and e-cigarette use) or (for visits 2-5) return unused supplies (patches and e-cigarette tanks). Subjects who do not complete each visit will still receive payment for the visits attended. Thus, subjects who attend five visits and hand in their take-home forms each time and also attend the follow-up visit will receive a total payment of $310. Subjects will not be compensated for the screening session.

CONSENT PROCESS

Because of the nature of this study and the amount of questionnaires that subjects are expected to complete, we do not recruit potential subjects who do not read, are blind or who do not read/understand English. We are not equipped to validate alternate versions of our questionnaires, most of which are not published. Questionnaires cannot be administered orally by a translator or by Technicians to illiterate or blind subjects because the data obtained would not be comparable to self-administered questionnaires.

RISK/BENEFIT ASSESSMENT

Conventional (combustible) cigarettes: Continuing to smoke carries significant health risks. Subjects enrolling in this study are not being asked to quit smoking over the course of the study, but will be exposed to no additional risk from their usual smoking behavior. Their exposure to harmfully and potentially harmful constituents in combustible cigarettes may decrease to the extent they use e-cigarettes as an alternative to combustible cigarettes.

Potential side effects of Nicotine patch: The nicotine patch poses very little risk and is approved for over-the-counter sales as a smoking cessation treatment. It is not being used as a cessation treatment in this protocol but the risks will be minimal. Insomnia and abnormal dreams are common and expected side effects associated with 24-hour nicotine patches. If a subject complains of disturbed sleep, he or she will be instructed to remove the patch at bedtime and apply a new one the next day at the usual time. Skin irritation may occur, although this will be minimized by changing the site of patch application daily. If a subject develops itching or a rash at the patch site, he or she will be advised to use 1% hydrocortisone cream on the affected area. Symptoms associated with nicotine toxicity include lightheadedness, dizziness, nausea, fainting and vomiting. A less likely side effect of nicotine patches is somnambulism.

Electronic Nicotine Delivery Systems (ENDS): ENDS, or "e-cigarettes," have been marketed in the U.S. since 2007 and have been used worldwide by millions of smokers. While the potential risks of long-term use of e-cigarettes are unknown, most experts agree that the constituents of e-cigarettes are less toxic than those of combustible cigarettes (Grana et al., 2014). Although it is conceivable that participants could receive an overdose of nicotine, this is extremely unlikely inasmuch as smokers can control the dose according to how they puff and inhale from the devices, as they do with conventional cigarettes. The main side effect that is anticipated with the relatively short 8-week duration of exposure to ENDS in the proposed project is mild irritation of the respiratory tract from inhalation of the propylene glycol and nicotine contained in the product. Should any clinically significant changes occur, the study physician will recommend discontinuation of ENDS use if it is indicated.

Needle stick / Blood drawing: The risks associated with venipuncture are minimal, and include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, and fainting are also possible, although unlikely.

Subjects will be monitored throughout the duration of the study for side effects and severe adverse effects (SAEs). They will be instructed to report any side effects to the study technicians, who will communicate these reports immediately to the medical staff. The most appropriate course of action will be determined, which may include options for dose reduction or termination of treatment. Participants will be reminded that they have the option to withdraw from the study at any time. Subjects will also be given the 24-hour emergency contact numbers in the event that side effects or adverse events occur between sessions. SAEs will be reported to the IRB and will be monitored until resolution or stabilization.

The sponsor for this study will ensure the investigational tobacco product is distributed only to qualified members of key personnel in accordance with this protocol.

SERIOUS ADVERSE EVENT REPORTING PLAN

The Principal Investigator will report all serious adverse events relating to the study in an expedited manner to the Duke University Health System (DUHS) Institutional Review Board (IRB) office, and all applicable regulatory authorities in accordance with the Center's standard operating procedures.

If the Sponsor-Investigator is notified that a study subject has a serious and unexpected adverse experience associated with the use of the investigational tobacco product, we will inform the IRB, NIDA, FDA, and all participating clinical investigators within a few days after initial receipt of the notification. In addition, we will notify the IRB, NIDA, FDA, and all participating clinical investigators of any serious or unexpected adverse experience associated with the tobacco product within a few weeks after initial notification. Reporting to NIDA will be performed using the Serious Adverse Event Tracking and Reporting System (SAETRS) at https://saetrs.nida.nih.gov; reporting to FDA will be performed using the Safety Reporting Portal (SRP) at https://www.safetyreporting.hhs.gov.

COSTS TO PARTICIPANTS

There are no costs to participants for taking part in this study. All the study costs, including any study medications and procedures related directly to the study, will be paid for by the research grant awarded to Duke University.

DATA ANALYSIS & STATISTICAL CONSIDERATIONS

The primary outcome measures will be the amount of combustible cigarette use and e-cigarette use in the last week of the 8-week exposure period. The main index of combustible cigarette use will be expired air CO, a highly sensitive and specific measure of smoke inhalation. As a secondary measure (at the first (V1) and final (V5) sessions), we will assess total urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), a metabolite of the tobacco-specific carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The half-life of NNAL is 10 days (Goniewicz et al., 2009), yielding a valuable index of sustained reductions in cigarette smoking. The half-life of expired air CO, in contrast, is 4.5 h (Sandberg et al., 2011). Self-reported cigarettes/day recorded on diaries will be a secondary index of cigarette consumption. The main index of e-cigarette use will be the number of cartridges consumed, based on self-report and counts of the number of unused e-cigarette tanks returned. We hypothesize (H1) that e-cigarette use will be higher, and concomitantly, combustible cigarette use will be lower, in the nicotine e-cigarette conditions compared to the zero-nicotine e-cigarette conditions (i.e., comparing Group 1 and Group 3 vs. Group 2 and Group 4) and also hypothesize (H2) that e-cigarette use will be higher, and concomitantly, combustible cigarette use will be lower, in the inhaled nicotine condition than the transdermal nicotine condition (i.e., comparing Group 3 with Group 2). These hypotheses will be evaluated using General Linear Modeling (GLM) techniques to assess the

significance of the nicotine factor and route-of-administration factor (and potential interactive effects), using a 2-tailed alpha=0.05. Covariates in the analysis of combustible cigarette use will include the amount of e-cigarette use, since that will affect the overall dose of nicotine received by subjects, as well as baseline combustible cigarette use, and baseline demographic and smoking history variables (the latter will also serve as covariates in the analysis of e-cigarette use as a dependent measure). We predict at least a moderate effect size (0.5) for each of the main effects, nicotine and route of administration, so that a sample size of 65 per group will yield at least 80% power to detect the hypothesized effects.

DATA & SAFETY MONITORING

Description of BP monitoring procedures after study enrollment

After study enrollment, if blood pressure during return sessions is above 160/100, then the following actions will be taken to enhance subject safety:

- If BP >210/100 with symptoms of malignant hypertension: stop experiment interventions and refer to appropriate medical treatment. Resume participation and continue to be monitored if BP is no greater than 140/100.
- If BP > 160/100 for 2 consecutive sessions, then CSC will provide either weekly BP checks or request that the participant have his/her BP checked weekly by PCP, local pharmacy, or home machine and call us with results. The physician assistant will discuss these results with the study physician.
- A blood pressure memo to file form will be completed if BP>160/100 for 3 readings per center approved procedure.

Data Safety Monitoring Plan (DSMP)

To address potential safety issues in addition to collection of the primary study outcomes, severe side effects and adverse events potentially associated with the study will be examined, recorded and then reported to the IRB in a manner consistent with Duke HRPP policies. The principal investigator will be responsible for monitoring data collection and safety of this study.

Data collection for this study will be carried out at the Durham clinical site of the Duke Center for Smoking Cessation (CSC). All members of the study team will complete research integrity ("code of conduct") and CITI (Collaborative Institutional Training Initiative) Human Research Curriculum and clinical laboratory safety training as required by Duke University Medical Center. All study staff who are involved in data collection, management, and processing will be thoroughly trained following standards of procedures prior to working on this project.

Study staff responsible for data collection will use a checklist for completion for each study visit of each participant. Missing Data Forms, along with explanations should missing data occur, will be completed by the study staff for each study visit.

Microsoft Access will be used for logging subject information (Enrollment Log, Visit Log, etc.). Data will be entered by the study staff. The key study personnel will further examine the computerized data entries and original records for accuracy and completion.

Emergency Unblinding

This is a blinded protocol such that all participants and all study personnel except for the Clinical Research Coordinator and the Research Program Leader are blinded to group allocation. During specific circumstances it will be necessary to unblind other study personnel, such as study team medical personnel. Emergency unblinding will occur under the discretion of the study physician (or one of the study physician assistants) in any situation in which unblinding is deemed necessary to ensure or promote the safety of a study participant. The decision to unblind for safety reasons may occur for a number of reasons and it is not possible to enumerate all potential circumstances. Examples of reasons for unblinding to ensure participant safety include situations in which it is necessary to know which study drugs the subject was taking in order to manage the side effect(s), advise the subject on the risk of future negative drug reactions, uncover potential safety information about the drug, and/or determine whether the adverse event is study related. In those situations, the Clinical Research Coordinator or Research Program Leader will inform the study physician (or physician assistant handling the event) of that subject's treatment condition. If unblinding occurs, that subject's data will be censored and will not be included in final data analyses.

DATA STORAGE & CONFIDENTIALITY

Any PHI collected prior to documentation of informed consent will be de-identified if the potential subject does not qualify for this study. Please refer to the "Request for Waiver of Documentation of Informed Consent".

Prior to any physical screening procedures, subjects will be informed, in their consent forms, of the data storage and confidentiality safeguards, which are practiced according to current HIPAA regulations. Study records that identify subjects will be kept confidential as required by law. Blood and urine specimens will be sent to LabCorp for processing. Name, date of birth, and gender will be included with each specimen. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Duke University Health System (DUHS) (except to LabCorp). For records disclosed outside of DUHS, subjects will be assigned a unique code number. The key to the code will be kept in a locked file in the PI's office separate from the locked file where the study records are stored.

During data collection, data for active subjects are kept at our offices located in Durham, NC.

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