TRIAL PROTOCOL

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Title: Impact of exclusive use of low nicotine cigarettes on compensatory smoking

Principal Investigator: Tracy Smith

NOTE: Protocol is Version 6 and is the final approved IRB protocol. Two protocol changes are not reflected but were implemented for all study participants: 1) intervention order was fixed for all participants (NNC→VLNC) rather than counterbalanced, and 2) unblinding wording for participants was changed to either “All of the cigarettes provided to you and all other participants during this hotel stay have a normal nicotine content. The nicotine content is about the same as what would be available in a typical cigarette purchased on the market today” (NNC) or “All of the cigarettes provided to you and all other participants during this hotel stay have a very low nicotine content. The nicotine content is about 97% less than what would be available in a typical cigarette purchased on the market today” (VLNC).

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ABSTRACT

Smoking is the leading cause of preventable death in the United States. In 2009, the Food and Drug Administration was given the authority to regulate tobacco products, including the authority to reduce the nicotine content of cigarettes to any non-zero level. A drastic reduction in nicotine content could reduce the prevalence of smoking. However, one of the primary concerns regarding nicotine reduction is that smokers would increase their smoke intake—either through increasing the number of cigarettes smoked per day or changing the way they smoke—to obtain more nicotine. Nicotine reduction clinical trials have generally not found evidence of compensatory smoking. However, most participants in low nicotine groups use non-study cigarettes, despite explicit instructions to use only the study cigarettes provided to them. Thus, it is possible that an FDA-mandated reduction in the nicotine content of cigarettes could lead to compensatory smoking when normal nicotine content cigarettes are no longer available for purchase. The aim of the proposed study is to test the impact of nicotine reduction on smoking behavior and smoke exposure when participants do not have access to normal nicotine content cigarettes. Participants will be confined to a hotel setting for two four-night stays during which time they only have access to the investigational cigarettes provided to them. During one hotel stay they will have access to investigational normal nicotine content cigarettes, and during the other hotel stay they will only have access to investigational very low nicotine content cigarettes. We have successfully utilized these procedures in our previous study to restrict access to non-study tobacco products (1). To assess whether smokers engage in compensatory smoking as a result of nicotine reduction, biomarkers of smoke exposure (expired carbon monoxide) and behavioral measures of smoking (cigarettes smoked per day, puff topography) will be compared between the two conditions.

PROJECT NARRATIVE

Smoking is the leading cause of preventable death in the United States. An FDA-mandated reduction in the nicotine content of cigarettes might reduce the health burden of tobacco by reducing the prevalence of smoking. The proposed project will test the impact of nicotine reduction on smoking behavior and smoke exposure in a setting where participants are restricted from using their usual brand cigarettes.

SPECIFIC AIMS

Cigarette smoking is the leading cause of preventable death in the United States. In 2009, the Family Smoking Prevention and Tobacco Control Act was passed, giving the FDA the authority to regulate tobacco products. One regulatory strategy that has been proposed is a drastic reduction in the nicotine content of cigarettes. Indeed, the FDA recently announced their intention to move forward with a potential nicotine reduction policy (2). Clinical data regarding nicotine reduction thus far have been encouraging. The largest nicotine reduction clinical trial to date was published in 2015 and showed that a reduction in nicotine content to 0.4 mg nicotine / g tobacco resulted in fewer cigarettes smoked per day, a reduction in measures of nicotine dependence, and an increase in quit attempts after the study was over (3).

One of the primary concerns regarding a nicotine reduction strategy is that smokers might alter their smoking behavior to maintain nicotine exposure (i.e., compensation)—either through changes in the number of cigarettes smoked per day or in how they smoke cigarettes. Compensation is well known to occur when smokers use “light” cigarettes (i.e., cigarettes that have reduced nicotine yield due to increased ventilation) (4). There is little evidence from clinical trials that switching to very low nicotine content (VLNC) cigarettes produces compensatory smoking behavior. However, during clinical trials, the majority of participants smoke

non-study cigarettes despite explicit instructions not to use any tobacco products other than the study cigarettes provided to them, and the rate of self-reported non-compliance is higher in the lower nicotine content groups (3, 5). The use of usual brand cigarettes during clinical trials could be masking compensation that would occur if smokers could no longer purchase normal nicotine content cigarettes, as would be the case following a mandated nicotine reduction policy. Thus, one hypothesis is that if access to normal nicotine content cigarettes were restricted, smokers would compensate for the reduction in nicotine. The likelihood of compensation is a critical issue for the FDA to understand given that compensatory changes in smoke exposure could have disastrous implications for public health.

In a prior study conducted under the direction of Dr. Smith (PI), 23 smokers were restricted to a hotel and exclusively smoked VLNC cigarettes provided to them by study staff for 4 days (1). In this setting, decreases in nicotine exposure confirmed that participants were not using non-study cigarettes. The purpose of the study was to characterize biomarkers of nicotine exposure when compliance with VLNC cigarettes is known, so there was no need for a control group that smoked normal nicotine content cigarettes in the same context. Relative to baseline, the number of cigarettes smoked per day increased by 54% (20.1 at baseline to 30.9) and carbon monoxide increased by 22% (18.6 ppm at baseline to 22.7 ppm). These data suggest that a reduction in nicotine content could result in compensatory smoking. However, smoking in the hotel may also have increased because participants were provided with cigarettes for free, had few competing activities, and were largely unconstrained by smoke-free environments. Without a control condition utilizing normal nicotine cigarettes in the same context, it is difficult to interpret changes in smoke exposure.

The goal of the present study is to assess whether smokers known to be exclusively using VLNC cigarettes engage in compensatory smoking behavior. Smokers will spend two five day / four night stays in a hotel setting during which time all of their cigarettes will be provided by study staff. We have requested to enroll up to 50 participants with the ultimate goal of having 20 eligible smokers who complete the hotel phase of the experiment. During one stay, participants will only have access to normal nicotine content cigarettes (NNC condition) and during the other stay participants will only have access to VLNC cigarettes (VLNC condition). We have successfully utilized these procedures in our previous study to restrict access to non-study tobacco products (1). Smokers' expectancies about nicotine can impact their smoking behavior, so participants will be told about the nicotine content of each condition's assigned cigarette. To assess changes in smoke exposure we will compare biomarkers of nicotine and smoke exposure and behavioral measures of smoking behavior between the two conditions.

Specific Aim 1: to assess whether exclusive use of VLNC cigarettes results in increased smoke exposure as measured by biomarkers of smoke and nicotine exposure including expired carbon monoxide (measure of short-term exposure to smoke) and cotinine (primary metabolite of nicotine).

Specific Aim 2: to assess whether exclusive use of VLNC cigarettes results in increases in behavioral measures of smoking including cigarettes smoked per day and total puff volume.

Hypothesis: In the context of exclusive VLNC use, participants will increase their smoke exposure relative to the NNC condition to compensate for the reduction in nicotine in VLNC cigarettes.

Alternative Hypothesis: Data will be consistent with recent nicotine reduction clinical trials showing that smokers in the VLNC condition will decrease their smoke exposure relative to the NNC condition.

A. SIGNIFICANCE

A1. Reducing the nicotine content of combustible tobacco to improve public health

In 2009, the Family Smoking Prevention and Tobacco Control Act provided the FDA with the authority to regulate tobacco products. An FDA-mandated reduction in the nicotine content of cigarettes might improve public health by reducing the prevalence of smoking. Evidence from clinical trials investigating nicotine reduction is encouraging. In the largest clinical trial to date investigating nicotine reduction, daily smokers who were randomly assigned to receive cigarettes with 0.4 mg nicotine /g tobacco smoked fewer cigarettes per day, scored lower on multiple measures of dependence, had lower levels of craving for their study cigarette, evaluated their study cigarette as having lower reinforcement value, and were more likely to make a quit attempt after the study was over (1, 8).

A2. Compensation as a result of nicotine reduction

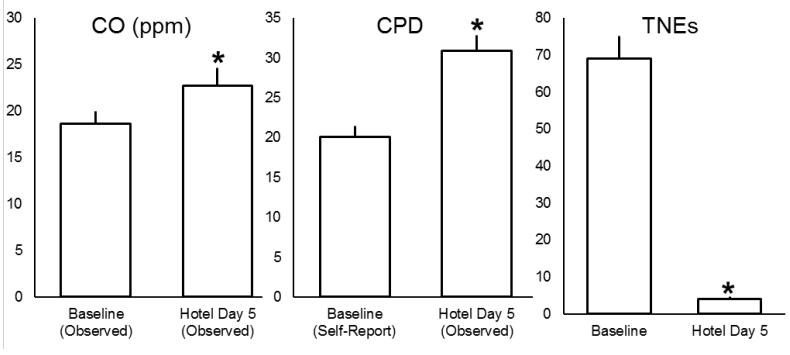
A critical concern regarding a mandatory nicotine reduction policy is that smokers might increase their smoke intake—either through increases in cigarettes smoked per day or changes in how they smoke cigarettes—to obtain more nicotine (i.e., compensation), negatively impacting public health. It is well known

that when smokers switch to highly ventilated cigarettes that deliver less nicotine (i.e., light cigarettes), they compensate for the reduction in nicotine yield, largely maintaining their nicotine exposure (4). However, data regarding VLNC cigarettes, which have a much lower nicotine yield as a result of a large reduction in the actual nicotine content of the cigarette, are less clear. Acute laboratory studies have shown that when smokers switch to VLNC cigarettes, they engage in compensatory changes in smoking behavior for the first few cigarettes (6, 7). However, clinical trials have not shown a sustained increase in smoke exposure associated with VLNC cigarettes (3, 8, 9). One possible reason that smokers in clinical trials do not compensate for the loss in nicotine may be that they can easily access normal nicotine content cigarettes.

A3. Most smokers in nicotine reduction clinical trials are not fully compliant

In clinical trials, smokers are given explicit instructions to only smoke the study cigarettes provided to them. However, despite these instructions, most use non-study cigarettes, and smokers in the low nicotine groups are more likely to self-report non-compliance than smokers in the control group (3, 10). These data suggest that when nicotine is reduced to a very low level, smokers use non-study cigarettes to compensate for the loss in nicotine. Thus, use of normal nicotine content cigarettes during nicotine reduction clinical trials may be masking compensatory smoking that would occur if normal nicotine content cigarettes were unavailable as part of an FDA-mandated reduction in nicotine content. However, an alternative hypothesis is that with exclusive VLNC use, smokers would be unable to obtain enough nicotine to reinforce behavior, resulting in a decrease in smoking. It is critical that researchers investigate whether compensation is a likely outcome of nicotine reduction by utilizing studies in which smokers use VLNC cigarettes but cannot access usual brand cigarettes. If compensation occurs, it would be important to consider factors that might mitigate that unintended consequence (e.g., alternative sources of nicotine) prior to implementing a nicotine standard.

A4. Scientific Premise



The majority of research in which smokers use VLNC cigarettes without access to usual brand cigarettes comes from lab based studies in which participants only smoke a few VLNC cigarettes (6, 7). There are a limited number of studies (discussed below) in which participants exclusively use VLNC cigarettes ad libitum for more than a few cigarettes. These studies have produced mixed findings and are limited in their generalizability to a post-regulation marketplace in a couple of key ways. First, these studies have provided cigarettes to participants for free, which is likely to increase smoking behavior in all participants regardless of nicotine content and could decrease the likelihood of observing compensatory smoking relative to an artificially inflated control condition. Second, most nicotine reduction studies, and all residential studies in which participants are known to be compliant with VLNC cigarettes, have kept participants blind to the nicotine content of the study product. While this approach isolates the impact of nicotine *per se,* it ignores the impact of smokers' expectancies about nicotine, which has been shown to impact how hard smokers are willing to work for cigarette puffs and smoking puff topography (11, 12). Putting aside those limitations, the data from prior studies are mixed as to whether compensatory smoking is likely to occur. In an inpatient study by Donny et al. (13), participants randomly assigned to VLNC cigarettes smoked *fewer* cigarettes per day, and had *decreased* expired carbon monoxide compared to participants smoking higher nicotine content cigarettes. However, this study did not include any urinary biomarkers of nicotine exposure, and participants were confined to a medical-like setting which has poor ecological validity. In contrast, McKinney et al. (14) found that participants restricted to using a low nicotine cigarette had *increased* toxicant exposure and smoked *more* cigarettes per day compared to baseline, but this study lacked a normal nicotine control group, and the reduced nicotine cigarette was higher in nicotine yield than the VLNC cigarettes being evaluated in recent clinical trials (3). The final study (1) was the hotel-based protocol mentioned above in which the goal was to develop biomarkers of compliance in our clinical trials. We sequestered groups of participants at a hotel to allow us to restrict access to only VLNC cigarettes in a more naturalistic and cost-effective setting. As expected, nicotine and related alkaloid exposure fell dramatically within days (Total Nicotine Equivalents (TNEs) shown above); however, compared to baseline (i.e., self-reported use in the real world), expired carbon monoxide increased by 22% and participants smoked 54% more cigarettes per day (see figure) (1). However, because the primary purpose of that study

was to characterize biomarkers of nicotine exposure in participants using only VLNC cigarettes, no control group was included, making it impossible to interpret the changes in smoking behavior. ***The goal of the present study is to use this novel hotel approach to assess compensatory smoking when participants smoke investigational cigarettes that either have a normal nicotine content or a very low nicotine content.*** We believe that a hotel sequestration is the strongest test of controlled access to experimental cigarettes while still maintaining an ecologically valid setting. Our prior study (1) is the only known study of VLNC within a restricted hotel setting. That study had some limitations (see above) that we now improve upon. Within the current study, participants will stay at a hotel with restricted access to only experimental cigarettes (VLNC or not). Participants will "purchase" cigarettes out of a study bank to model real world smoking and reduce the likelihood of a ceiling effect that might mask compensation. Additionally, the present study will provide participants with information about the nicotine content of the cigarettes in each condition to investigate the combined impact of nicotine reduction and smokers' knowledge about that reduction.

B. INNOVATION

The proposed study will investigate the impact of nicotine reduction using a protocol that closely models a post-regulation environment using three innovative strategies. First, the hotel setting is a highly novel and cost-effective approach to investigating the impact of nicotine reduction (and possibly other regulatory changes) in a naturalistic context where the tobacco marketplace can be controlled. Second, the present study will investigate the combined impact of nicotine reduction and smokers' knowledge about nicotine reduction—an approach rarely used in nicotine reduction studies and never in a study that eliminated access to non-study cigarettes. Finally, the present study will require participants to "pay" for each cigarette using a study bank, testing the impact of nicotine reduction in the context of normally priced cigarettes for the first time. Requiring participants to pay for each cigarette they smoke will also prevent smoking rate from being artificially inflated due to free cigarettes, which could prevent us from observing any potential compensation (i.e., ceiling effect).

C. APPROACH

C1. Overview

We will consent 50 participants with the ultimate goal of having at least 20 eligible smokers complete the hotel phase of the experiment. Smokers will be confined to a hotel for two hotel stays (five days/ four nights each) during which they will only have access to the investigational cigarettes provided to them. During one stay participants will receive cigarettes with 15.8 mg nicotine / g tobacco (normal nicotine content, NNC condition), and during the other stay participants will receive cigarettes with 0.4 mg nicotine / g tobacco (very low nicotine content, VLNC condition). Participants will enter the hotel in groups of 10 and everyone in a given stay will receive the same investigational cigarette, to mimic a regulatory change that would occur at the population level and to preserve the nicotine content manipulation in the event of sharing cigarettes (which is discouraged). The first aim will assess measures of smoke and nicotine exposure including urinary cotinine and expired carbon monoxide. The second aim will assess behavioral measures of smoking including cigarettes smoked per day and puff topography.

C2. Participants

Twenty daily smokers will be recruited from the Medical University of South Carolina through social media, TV, bus, and craigslist advertisements. In Dr. Smith's prior hotel-based study (4), we did not have difficultly recruiting participants for a single four-night hotel stay, and do not anticipate any difficulties here. Participants enter the hotel in groups of 10. We will recruit up to eight additional participants who will serve as alternates. They will be available during the hotel week in case another eligible participant is unexpectedly unable to attend the hotel phase. Alternate participants will receive $150 for their time if they are not needed.

Inclusion criteria will include: a) male or female participants who are at least 18 years old and have been smoking between five and thirty cigarettes daily for the past month (CO > 8, if CO ≤ 8 ppm, then NicAlert test of 6), and b) willing to stay in the hotel for two four-night stays during the prearranged dates. Smokers using more than thirty cigarettes per day are excluded to ensure we can observe an increase in smoking in all participants. Exclusionary criteria include a) interested in quitting smoking in the next month, b) unwilling to use research cigarettes as part of the trial, c) use of smokeless, hookah, cigars, e-cigarettes, or tobacco products besides cigarettes ≥ 10 days in the past 30, d) Binge drinking ≥10 days in the past month or self-reporting that it would be difficult to abstain from drinking while in the hotel, e) self-reported illicit drug use ≥ 10 days in the past month, positive urine toxicology (excluding marijuana), or self-reporting that it would be difficult to abstain from illicit drug use while in the hotel, f) pregnant, trying to become pregnant, or breastfeeding, g) currently using nicotine replacement therapies or other pharmacotherapies as a cessation aid, h) current or recent (past

month) suicidal ideation, or j) new diagnosis, difficulty with, or seeking medical attention for the following diagnoses in the last three months: heart attack, stroke, arteriosclerosis, heart disease, hypertension, emphysema, asthma, COPD, or cancer

We will also utilize a respondent-driven (i.e., RDS, referral) sampling program. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Participants will be provided with advertisement cards that they may give to friends or acquaintances that they think would be interested in the study. Participants will be compensated $10 for every person referred, using one of their cards, who is study eligible and completes the screening visit. Individuals referred to the study may not reside in the same household as the study participant while the study participant is enrolled.

We will also recruit as part of the Project Quit Collaborative, a group of smoking researchers on MUSC campus that recruit participants through a common website and a common phone number and texting number. When potential participants go to the Project Quit website, this study will be listed as an actively recruiting study that participants can inquire about if they call the Project Quit number. Participants who are interested in this study will be referred to our study team by Project Quit staff. Wording for the website has been submitted under the Advertisements section of this protocol. The Project Quit website and collaborative have been previously reviewed and approved by MUSC Brand, IRB 1, and IRB 2 for protocol numbers 14398, 64367, 60290, 52793, and 48152. The website is www.projectquitsc.com.

C2a. Menthol status and gender. Research suggests that there may be gender differences in the impact of nicotine on reinforcing smoking behavior, with nicotine playing a more critical role in maintaining smoking behavior for men than for women (15-17). Thus, one hypothesis would be that when nicotine is reduced, men would be more likely to engage in compensatory smoking to adjust for the loss in nicotine. Menthol content may also influence compensatory smoking. Menthol has been known to reduce the harshness of cigarette smoke(18), and thus menthol smokers may find it easier to compensate for the loss of nicotine by increasing puff volume or cigarettes smoked per day (CPD). In this study, we will monitor the rates of recruitment for these categories and attempt to balance the numbers of men/women and menthol/non-menthol smokers. We may cap recruitment of one of these categories if recruitment is unbalanced (e.g., >75% in one category). Smokers will be provided with menthol or non-menthol cigarettes that match their preference.

C3. Cigarettes

Spectrum cigarettes will be ordered through NIDA (NOT-DA-14-004). These cigarettes are manufactured by 22nd Century, Inc. and managed by the Research Triangle Institute. During the control week, participants will receive NRC600/601 (non-menthol/menthol) which has a nicotine content of approximately 15.8 mg/g tobacco (reported nicotine yield (ISO): 0.8 ± 0.15 mg; tar yield:10.5 ± 1.5). During the VLNC week, participants will receive the NRC102/103 (non-menthol/menthol) which has a nicotine content of approximately 0.4 mg/g tobacco (reported nicotine yield (ISO): 0.03 ± 0.0 mg; tar yield: 9 ± 1.5). Ventilation is the same across the two products. Dr. Smith has used these products in several projects. These products require that we obtain approval as Investigational Tobacco Products from the FDA because they are not commercially available. The FDA provided this approval on January 18, 2018 (see ITP uploaded in IRB Protocol forms).

C4. Hotel

The Hotel Phase portion of this study will take place at a local Charleston hotel. The hotel will be chosen using the following criteria: 1) allows smoking in select hotel rooms that will be used for participants' guest rooms, 2) is in a relatively remote area of Charleston (few businesses within walking distance), 3) has a meeting area that can be utilized by the study for the purposes of data collection and serving meals, 4) in the appropriate price range. Amenities such as a daily free breakfast and hotel gym are preferred but not required. Hotel staff will not be involved in data collection, and will interact with the participants only to the extent necessary (providing with room keys, etc). We have arranged to have this study conducted at the Quality Inn Coliseum in North Charleston. In the event that we need to choose another hotel, we will use the criteria above.

Study staff will search participants' belongings prior to being transported to the hotel, and any non-study tobacco products or alcohol will be confiscated and returned upon completion of that hotel phase. Participants who bring any illegal substances, or weapons to the lab on the day of departure to the hotel will be dismissed from the study. Participants will be transported to and from the hotel by a shuttle service.

Participants will be asked to remain on hotel property and will not be permitted to have any outside visitors. Each participant will receive their own hotel room, unless two participants know each other and request a room together prior to starting the study. Participants will be provided with all meals in the hotel either by the hotel or using an outside catering company. We will provide entertainment (e.g., books, movies, crafts, area to socialize) but participants will be encouraged to bring laptops, cell phones, and other items for down time between study tasks. The hotel is a strength of the proposed protocol because it allows us to investigate the impact of nicotine reduction in a comfortable and social context that mimics the "real world" in which people smoke. Study tasks will take place in a hotel meeting or activity room, or a separate guest room if a hotel meeting room is not available. Two or more staff members will be at the hotel at all times. Participants will be required to remain in their hotel rooms between 9:00PM and 7:00AM unless there is an emergency (e.g., fire). We have successfully utilized these procedures in our previous study to restrict access to non-study tobacco products (1).

C5. Instructions

Participants will be told that while in the hotel, they will be permitted to use research cigarettes provided to them, but that they will not be permitted to use other nicotine or tobacco products. During their screening session, participants will be told that we are investigating a range of nicotine contents and that they will receive cigarettes with different nicotine contents during their two hotel stays. When participants arrive at the hotel, they will be told the condition for that week.

C6. Product Distribution

Participants will have the opportunity to "purchase" Spectrum cigarettes at each "check in" from study staff using a study bank. Each cigarette will cost $0.30 (close to the national average for cigarettes). Participants will begin the study with $72.00 (enough for 60 CPD) to spend on cigarettes during the hotel stay, and will be told that any money they choose not to spend on cigarettes will be given to them at the end of the study. Participants do not have to purchase any cigarettes, and if a participant chooses to abstain from smoking while in the hotel, it will not affect their study participation or financial compensation in any way.

C7. Procedures

Study participation consists of a screening visit and two four-night stays in the hotel.

C7a. Screening visit. After obtaining informed consent, screening assessments will be completed (measures described below). At the end of the session, eligible participants will be scheduled for two hotel stays. It will be stressed to participants that it is critical that they attend both hotel stays, and we have provided a completion bonus to maximize the likelihood of study completion. In our prior study (1), 100% of our participants completed the entire hotel protocol. A baseline puff topography assessment will be completed for eligible participants using participants' usual brand cigarette. Puff topography provides an analysis of smoking behavior including changes in the rate or volume of inhalation which can influence smoke exposure and nicotine delivery of cigarettes.

C7b. Hotel phase. Participants will return to the lab on the morning of each hotel stay. Participants will complete a Timeline Follow Back Assessment about their tobacco use over the previous 14 days, and we will collect a first void urine for baseline assessment. We will also obtain an expired carbon monoxide sample.

Participants will arrive at the hotel and have their first opportunity to buy cigarettes at 4PM on Hotel Day 1. While at the hotel, participants will have "check in" times of 8AM, 12PM, 4PM, and 8PM. Check-ins will be used to collect physiological assessments, collect self-report questionnaires, and for participants to purchase more cigarettes if needed. Measures at the hotel are designed to assess the safety of the participants using the study product, the impact of nicotine reduction on physiological and behavioral measures of smoke exposure, and the impact of nicotine reduction on other key measures like withdrawal, craving, and reinforcement value. Participants will return all unused cigarettes and depart the hotel at 12PM on Hotel Day 5. Participants will spend approximately 96 hours (four 24-hr periods) in the hotel. A puff topography assessment will be completed each day by having participants smoke one of the research cigarettes through a device that measures how they smoke cigarettes. Puff topography provides an analysis of smoking behavior including changes in the rate or volume of inhalation which can influence smoke exposure and nicotine delivery of cigarettes.

C7c. End of Study Procedures: After a participant has completed all study procedures during the second hotel week and has been paid for participation, a research assistant should read the following script:

"Before you go, we want to encourage you to try to be abstinent from smoking. Although the study is over, you may find it easier to quit as a result of your participation. We would like to provide you with some resources should you decide to try to abstain from smoking. Please also feel free to consult with your physician and use any medications he/she deems appropriate. Thanks again for your participation."

C8. Follow-up Call: Approximately 30 days after the end of the second hotel week, study staff will call each participant and complete a short follow-up call. During this call, we will assess current tobacco use and any quit attempts since the study ended. We will also ask participants whether they used any non-study tobacco products during their hotel stays. If participants self-report non-study tobacco use while at the hotel, we will ask about the frequency and rate of use, which products were used, and how participants obtained those products. Participants will be paid for completing the follow-up call regardless of whether they self-report non-study tobacco product use.

C9. Spontaneous quit attempts

Participants will not be eligible to participate if they intend to quit smoking as assessed at screening. If a participant chooses to abstain from smoking while at the hotel, they can continue their stay in the hotel with no consequences. If a participant chooses to make a quit attempt after their screening visit but before either of their visits to the hotel, they will be withdrawn (to avoid interfering with that quit attempt) and replaced.

C10. Compensation for Study Participation

Participants will receive $25.00 for the screening visit, $55.00 for each hotel day ($550.00 total), and a completion bonus for finishing both hotel stays ($300.00). Participants will earn $10 for completing the follow up call. Participants who complete the entire study will earn $885.00. Participants will also earn a variable amount of money depending on the value of their study bank at the end of the study. Based on our prior experience, we estimate this will be approximately $96 per participant across the two weeks (assuming participants smoke one pack/day on average).

Participants who are ineligible during the screening visit will still earn the $25 for completing the visit as long as they pass the drug test, pass the breath/urine tests indicating smoking status, are available during the prearranged hotel dates, and are willing to smoke research cigarettes as part of the study. Participants who are ineligible for the reasons listed above will earn $10 and will not complete the remainder of the screening visit. Participants may also earn $20 for each person they refer to the program who is eligible, enrolls, and enters the hotel phase. Participants will be provided with referral cards to distribute.

C11. Measures. The table below summarizes the timeline for screening (Scr) and hotel day (HD) measures, each of which is described below.

Measure	S	HD1			HD2				HD3				HD4				HD5	
		Lab	4P	8P	8A	12P	4P	8P	8A	12P	4P	8P	8A	12P	4P	8P	8A	10A
Identifying Information Form	X																	
Demographics Questionnaire	X																	
Tobacco Use History	X																	
Smoking Cessation Questionnaire	X																	
MINI	X																	
Stages of Change	X																	

Alcohol Use Questionnaire 1 month	X																	
Drug Use Questionnaire 1 month	X																	
Brief Medical History	X																	
Pregnancy Test	X	X																
Urine Drug Screen	X	X																
Health Changes V1		X																
Health Changes V2																	X	
CESD-V1		X																
CESD-V2																	X	
Timeline Follow back		X																
Carbon Monoxide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FV Urine		X			X				X				X				X	
Collect 24-hr Urine						X				X				X				X
Opportunity to purchase cigs			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect Time-stamped Cig Butts						X				X				X				X
Puff Topography-Usual Brand	X																	
Puff Topography-Study Cigarette					X				X				X				X	
MNWS		X			X				X				X				X	
QSU-Usual Brand		X															X	
QSU-Study Cigarette					X				X				X				X	
CES-Usual Brand		X																
CES-Study Cigarette				X													X	
Cigarette Purchase Task-UB		X															X	
Cigarette Purchase Task-Study Cigarette																	X	

Perceived Health Risks-Usual Brand		X															X	
Perceived Health Risks-Study Cigarette																	X	
Predicted Behavior Questionnaire																	X	
SCQ-A (before they try them, but after unblinding)			X															
FTND V1		X																
FTND V2																	X	
Brief WISDM-V1		X																
Brief WISDM-V2																	X	
Knowledge and Beliefs about Nicotine		X																
Knowledge and Beliefs about Smoking		X																
Qualitative Interview															X			
Delay Discounting													X					
End of Hotel Week Assessment																		X
30-d Follow-up Call																		

The following questionnaires will be administered via paper and kept as source documents:

1. Identifying Information form: will include the participant's subject identifier, name, address (including the county of residence), e-mail address, phone number, age, date of birth, and social security number

The following questionnaires will be completed by the participant using Redcap:

1. Demographics Questionnaire: which will assess age, gender, ethnicity, race, education, income, marital status, and employment history
2. Alcohol Use Questionnaire 1 month will assess alcohol use and binge drinking over the last month.
3. Stages of Change: a measure of intention to quit smoking
4. Minnesota Nicotine Withdrawal Scale: a measure of nicotine withdrawal.
5. Questionnaire of Smoking Urges—Usual Brand: which measures the urge to smoke participants' usual brand cigarette

6. Questionnaire of Smoking Urges—Study Cigarette: which measures the urge to smoke participants' assigned study cigarette.
7. Cigarette Evaluation Scale—Usual Brand: which measures responses to participants' usual brand cigarettes (e.g., reward satisfaction)
8. Cigarette Evaluation Scale—Study Cigarette: which measures responses to participants' assigned study cigarettes (e.g., reward satisfaction)
9. Cigarette Purchase Task—Usual Brand: will be used to generate demand curves. The Cigarette Purchase Task is considered to be a measure of reinforcement value. Participants report the number of usual brand cigarettes that they would consume in a day if cigarettes were a variety of prices.
10. Cigarette Purchase Task—Study Cigarette will be used to generate demand curves. The Cigarette Purchase Task is considered to be a measure of reinforcement value. Participants report the number of assigned study cigarettes that they would consume in a day if cigarettes were a variety of prices.
11. Perceived Health Risks—Usual Brand: a measure of the perceived health risks of participants' usual brand cigarette
12. Perceived Health Risks—Study Cigarette: a measure of the perceived health risks of participants' assigned study cigarette
13. Predicted Behavior Questionnaire: a questionnaire designed to assess participants predictions about their tobacco use if the research cigarettes were the only cigarettes available for purchase (a potential policy scenario).
14. Smoking Consequences Questionnaire-Adult is a validated measure of smoking expectancies and will be used to assess participants expectancies for very low nicotine content and normal nicotine content research cigarettes.
15. Fagerstrom Test for Nicotine Dependence (FTND) V1: A validated measure of nicotine dependence. At baseline, participants complete this questionnaire about their smoking habits.
16. Fagerstrom Test for Nicotine Dependence (FTND) V2: A validated measure of nicotine dependence. At the end of the hotel week, participants complete this questionnaire but are instructed to only think about their smoking over the last 24 hours.
17. Wisconsin Inventory of Smoking Dependence Motives (WISDM) Brief V1: A validated measure of nicotine dependence. At baseline, participants complete this questionnaire about their smoking habits.
18. Wisconsin Inventory of Smoking Dependence Motives (WISDM) Brief V2: A validated measure of nicotine dependence. At the end of the hotel week, participants complete this questionnaire but are instructed to only think about their smoking over the last 24 hours.
19. Knowledge and Beliefs about Nicotine: A measure assessing participants knowledge and perceptions of nicotine as an addictive constituent in tobacco and about the health consequences of nicotine
20. Knoweldge and Beliefs about Smoking: A measure assessing participants' knowledge and perceptions about the health consequences of smoking
21. Delay Discounting: A validated measure of impulsivity in which participants make hypothetical decisions about whether they would prefer a small amount of money now or a larger amount of money after a variable length of time.
22. End of Hotel Week Assessment After participants have been paid for study participation during each hotel week, they will complete one additional assessment that assessed their use of non-study tobacco products during the hotel week.

The following questionnaires will be completed as an interview and entered into Redcap by study staff:

1. Tobacco Use History Questionnaire: which measures variables such as smoking amount, cigarette brand, age of initiation, number of quit attempts, duration of quit attempts, and duration of smoking
2. Smoking Cessation Questionnaire to assess use of nicotine replacement therapy or smoking cessation medications to help participants quit smoking
3. Drug Use Questionnaire 12 + 1 month: measures drug use over the last 12 months and 1 month
4. Health Changes Questionnaire V1: assesses health changes since participant's last visit
5. Health Changes Questionnaire V2: assesses health changes since entering the hotel.
6. Timeline Followback: assesses tobacco use in the last two weeks.
7. Mini International Neuropsychiatric Interview (MINI) suicide subscale: to evaluate suicide risk
8. Brief Medical History: to assess current diagnoses, symptoms, and past health problems

9. Follow-up Call: Approximately 30 days after the end of the second hotel week, study staff will call each participant and complete a short follow-up call. During this call, we will assess current tobacco use and any quit attempts since the study ended. We will also ask participants whether they used any non-study tobacco products during their hotel stays. If participants self-report non-study tobacco use while at the hotel, we will ask about the frequency and rate of use, which products were used, and how participants obtained those products. Participants will be paid for the call regardless of whether they self-report non-study tobacco product use.

The following questionnaires will be completed as an interview, tape recorded with the permission of the participants, and transcribed later:

1. Qualitative Interview: In order to better understand participants' subjective experiences in the hotel and their opinions and reactions to a potential regulatory nicotine reduction policy, a 15-20 minute qualitative interview will be completed.

The following physiological measures will be entered into Redcap by study staff:

1. Urine Pregnancy Test (HCG detection): will be performed for female participants with childbearing potential.
2. Urine Drug Screen: will be performed to assess for the presence of illicit drugs including marijuana, cocaine, opiates, benzodiazepines, barbituates, amphetamines, methadone, methamphetamines, tricylclic antidepressants, and PCP (positive test for marijuana or tricylclic antidepressants acceptable).
3. Expired Carbon Monoxide (CO) levels will be assessed using a Smokerlyzer Micro + CO meter (Bedfont Instruments), a reliable and valid measure of recent smoking. Two carbon monoxide samples will be collected at each sample, and if the two samples differ by more than two ppm, a third sample will be collected. The final CO outcome will be the average of the two (or three) samples.
    a. Nic Alert Strips: will be used to assess cotinine levels if a participant's carbon monoxide reading is less than or equal to 8.
4. First Void Urine: A urine sample participants collect of their first void urine from that morning using a urine collection cup provided by the lab. This urine will be stored at the Clinical Neuroscience Laboratory at MUSC and shipped to the Centers for Disease Control for testing of exposure to tobacco and tobacco smoke. Samples sent to the CDC will be coded, and the key linking codes to identifying information will remain at MUSC. The CDC will destroy any residual samples once analyses are complete.
5. 24-hour Urine: Participants will collect all urine in the hotel using collection containers provided by the lab. Participants will return their urine and receive a new container every 24 hours. This urine will be stored at the Clinical Neuroscience Laboratory at MUSC and shipped to the Centers for Disease Control for testing of exposure to tobacco and tobacco smoke. Samples sent to the CDC will be coded, and the key linking codes to identifying information will remain at MUSC. The CDC will destroy any residual samples once analyses are complete.

Opportunity to purchase cigarettes: Participants will have the opportunity to "purchase" cigarettes from hotel staff at each check in.

Cigarette Butt Collection: Participants will be provided with a plastic bag in which to collect their cigarette butts. Participants will return their bag and receive new bags every 24-hrs. The first butt of each week and the first butt of each day will be kept separate.

Puff Topography: Participants will complete a puff topography assessment in which they smoke a cigarette through a CReSS device that provides an analysis of smoking behavior including changes in the rate or volume of inhalation which can influence smoke exposure and nicotine delivery in cigarettes.

C11a. Outcomes:
Primary outcomes:

1. **Average expired carbon monoxide over the last 24 hours in the hotel.** Carbon monoxide is on the FDA's list of harmful and potentially harmful constituents (19). Expired carbon monoxide can be measured intensively in this setting and is a well-validated measure of smoke exposure.
2. **the total number of cigarettes smoked at the hotel** (defined as the # cigarettes purchased at the hotel *minus* # returned at the end of the hotel stay)

Secondary outcome:

1. total number of cigarettes smoked at the hotel (defined as the number of cigarette butts collected during the hotel stay)
2. total puff volume (puff count * average puff volume for a single cigarette smoked through the CReSS micro device on Hotel Day 5)
3. Cotinine (the primary metabolite of nicotine) at baseline and Day 5 using urine to describe nicotine exposure and calculate a compensation index (i.e., the logarithmic change in nicotine exposure given the logarithmic change in nicotine content between products). The final urinary cotinine sample will also be utilized to confirm exclusive use of VLNC cigarettes in the VLNC condition (<2.69 nmol/ml, (1)). Cotinine analyses will be conducted by the Clinical Neuroscience Laboratory at the Medical University of South Carolina. Aliquots of all urine samples will be stored at the Clinical Neuroscience Laboratory for the possibility of conducting additional analyses if needed.
4. Withdrawal (MNWS) scores
5. Depressiong symptoms (CESD)
6. Craving (QSU) of both study cigarettes and usual brand cigarettes
7. Demand (parameters derived from purchase task) for usual brand and study cigarettes
8. Product appeal and reward (CES)
9. Changes in dependence (FTND and WISDM)

C11b Storage of biological specimens. Urine samples will be stored for future analysis. A section has been added to the consent form clearly describing the storage of biological speciments. Samples will be stored in the Clinical Neuroscience Laboratory at the Medical University of South Carolina. Samples will be deidentified. We will also store collected cigarette butts for potential future analysis.

C12. Statistical analysis, power calculations and predicted outcomes

For *Aim 1,* we will test the impact of cigarette nicotine content on physiological measures of smoke exposure using a linear mixed model with fixed effects for nicotine content, period, and order, and random effects for subject and group. Physiological outcomes are expected to be skewed and will be log transformed. The *primary outcome* is average expired carbon monoxide over the last 24 hours. A secondary analysis will be conducted using the area under the curve (AUC) for expired carbon monoxide across time points. For *Aim 2,* we will test whether nicotine reduction impacts behavioral measures of smoking behavior using the approach described above. Outcomes include average cigarettes smoked per day (total hotel cigarettes / 4) and total puff volume.

We will conduct exploratory tests of the impact of menthol status and gender on each outcome, although we are not powered to detect these effects. Future studies may follow up on gender or menthol effects we observe but cannot detect statistically. The within-subjects design should minimize variability, but we will collect baseline measures for all key outcomes, which can be included in analyses if necessary.

A power analysis revealed that a sample size of 20 smokers will provide 80% power to detect an effect size of 0.65 with an alpha of 0.05, which would correspond to a 20% increase in expired carbon monoxide (note we may enroll up to 50 participants in expectation of participants who do not meet eligibility criteria or withdraw). A 20% change in smoke exposure is consistent with the increase in smoke exposure and cigarettes smoked per day that is observed in experimental studies where smokers are switched to a cigarette with a lower nicotine yield (i.e., a light cigarette) (4, 19, 20). This sample size will provide power to detect a similar increase in remaining outcomes including cigarettes smoked per day and total puff volume.

C13. Scientific rigor considerations

Each participant will serve as their own control by completing a VLNC and NNC condition, in which all variables are held constant except the nicotine content of Spectrum cigarettes and the information that participants receive about nicotine content. Study staff will follow detailed protocols and scripts to standardize procedures. The order of conditions will be counterbalanced between the sets of 10 participants that complete the hotel stays together. Analyses will follow an a priori statistical analysis plan including rules for identifying

outliers and the use of a blinded third party for data cleaning as needed. Sample size was determined via a power analysis.

C14. The National Institutes of Health now considers all ongoing clinical research to be in possession of a Certificate of Confidentiality. With this certificate, the researchers cannot be forced to disclose information that may identify the participants, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demand for information that would identify the participants, except as explained below. The certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet requirements of the Federal Food and Drug Administration. The Certificate of Confidentiality does not prevent the participant or a member of their family from voluntarily releasing information about themselves and their involvement in the research. If an insurer, employer, or other person obtains the participant's written consent to receive research information, then the researcher may not use the Certificate to withhold that information. The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without consent, information that would identify the individual as a participant of the research project in instances such as evidence of child abuse or a participant's threatened violence to self or others.

PROTECTION OF HUMAN SUBJECTS

Risks for Human Subjects

Justification for using human subjects. Human subjects are essential in determining tobacco/nicotine product use patterns that may result if smokers had access to only VLNC cigarettes.

Inclusion and exclusion criteria, characteristics of the population and sample size: A total of 20 male and female subjects will be enrolled into this study over the course of 2 years. Enrolling this number of subjects is reasonable for our lab, which previously enrolled 31 participants over the course of two months in a similar study.

Subject Recruitment Timeline (Study Total N=20)

	Year 1: Sept-Feb	Year 1: March-Aug	Year 2: Sept-Feb	Year 2: March-Aug
Start-up				
Recruitment/ Enrollment		N=10	N=10	
Data Clean up and Analysis				

Inclusion criteria will include the following:

a) male or female participants who are at least 18 years old and have been smoking between five and thirty cigarettes daily for the past month (CO > 8, if CO ≤ 8 ppm, then Nic Alert test of 6), and
b) willing to stay in the hotel for two four-night stays during the prearranged dates.

Exclusionary criteria are designed to enroll relatively healthy smokers who are not interested in quitting smoking. They include:

a) interested in quitting smoking in the next month,
b) unwilling to use research cigarettes as part of the trial,
c) use of smokeless, hookah, cigars, e-cigarettes, or tobacco products besides cigarettes ≥ 10 days in the past 30,
d) Binge drinking ≥10 days in the past month, or reporting that it would be difficult to abstain from alcohol use while in the hotel
e) self-reported illicit drug use ≥ 10 days in the past month or positive urine toxicology (positive toxicology screen for marijuana acceptable), or reporting that it would be difficult to abstain from illicit drug use while in the hotel
f) pregnant, trying to become pregnant, or breastfeeding,
g) currently using nicotine replacement therapies or other pharmacotherapies as a cessation aid,
h) current or recent (past month) suicidal ideation,
i) new diagnosis, difficulty with, or seeking medical attention for the following diagnoses in the last three months: heart attack, stroke, arteriosclerosis, heart disease, hypertension, emphysema, asthma, COPD, or cancer.

Recruitment and retention plan. Subjects will be recruited through various media (internet, newspaper, radio, social media), flyers around college campuses, trade schools, and coffee shops.

We will maximize retention of the subjects by compensating them for their time. We will provide a respectful environment for the subject and train personnel on methods for minimizing subject drop-outs.

All participants will complete a VLNC hotel condition and a NNC hotel condition (i.e., within-subjects design). The content of the VLNC cigarette will be 0.4 mg/g nicotine. In a previous study that we conducted, a similar cigarette was found to lead to reduced smoking, nicotine exposure and dependence, and increased quit rates. The content of the NNC cigarette will be 15.8 mg/g nicotine. In the same previous study, we found that this cigarette led to an increase in the number of cigarettes smoked per day, but this increase was temporary and smoking returned to normal after the completion of the trial. It is possible that this study will produce less of an increase in smoking behavior because participants will “pay” for each cigarette using a study bank rather than having cigarettes provided for free as they were during the previous clinical trials.

Study sites. Research will be conducted at the Medical University of South Carolina (PI: Tracy Smith), and will utilize a local hotel for the hotel phase of the experiment. Dr. Smith is mentored by Dr. Matthew Carpenter, (CO-I), and the study team includes one month/year of support for four staff members. Dr. Smith will oversee the day-to-day operation of the study. All personnel will be trained on study procedures, human protection issues and regulatory requirements. Biosamples will be transferred to the Clinical Neuroscience Laboratory at the Medical University of South Carolina with no identifying information other than the sample and subject identifiers.

Sources of material. At screening, subjects will be asked to provide information on their tobacco use history. During the study, subjects will be required to complete a number of questionnaires (see above). Subjects will need to submit breath samples for alveolar carbon monoxide. Subjects will also submit urine samples. Access to identifying subject information for subjects will be kept locked in a secure area. No record of this identifying information will leave the premises. Any data from the subjects posted on a secure website will be de-identified.

Potential Risks.

Risks include breach of confidentiality, issues related to coercion, and risks related to smoking the study cigarettes.

1) **Issues Related to Coercion**: Coercion is a possible risk due to monetary compensation for participating in this study. The likelihood of this risk is low because the compensation is commensurate

with the amount of time and effort required for this study, as described below under Adequacy of Protection against Risk.

2) **Breach of Confidentiality:** Study data include biological measures of cigarette smoking, pregnancy and illicit drug use. The likelihood of breach of confidentiality is low as we will take precautions to minimize this risk as described below under Adequacy of Protection against Risk.

3) **Risk of fire:** Smoking cigarettes inside an enclosed structure (e.g. house, apartment, hotel room) can increase the chances of starting a structural fire. To reduce this risk, participants will be instructed avoid smoking under conditions that might increase the chance of starting a fire (e.g. in bed).
4) **Smoking Cigarettes:** All cigarettes are detrimental to a person's health and can lead to significant medical problems including:
    a. **Cardiovascular Diseases**: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    b. **Respiratory Diseases**: Emphysema, bronchitis, and chronic airway obstruction
    c. **Cancers**: Cancers of the lung, bladder, cervix, esophagus, kidney, larynx, mouth, pancreas, throat, and stomach; leukemia
    d. **Other Health Risks Associated with Smoking**: Including but not limited to infertility, lower bone density in postmenopausal women, and hip fracture in women
    e. **Risk to Fetus:** Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), and early childhood behavioral problems.
    f. **Smoking and oral contraceptives in women:** Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician.
    g. **Death**
5) **Smoking Study Cigarettes:** Smoking the study cigarettes could cause some minor adverse health effects such as headaches or experience withdrawal symptoms, which are listed below. Due to the altered nicotine levels, there could be a change in cigarette use including the manner in which smoke is inhaled. Participants may also experience increases in levels of carbon monoxide, a gas from smoke.
    a. **Smoking Withdrawal:** Participants may experience smoking withdrawal symptoms during this study. These symptoms can include anger, irritability, frustration, anxiousness, nervousness, depressed mood or sadness, desire or craving to smoke, difficulty concentrating, increased appetite, hunger or weight gain, insomnia, problems sleeping or awakening at night, restlessness, impatience, constipation, dizziness, coughing, dreaming or nightmares, nausea, and sore throat. These feelings can be uncomfortable but are typically of minimal risk.
    b. **Returning to Regular Smoking**: It is possible that if when participants return to smoking their usual brand of cigarette they may experience mild and transient nausea, dizziness, and lightheadedness.
    c. **Changes in blood pressure and/or heart rate:** Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate.
    d. **Changes in mood, emotions and psychiatric symptoms**: Smoking and nicotine can affect mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
    e. **Smoking and medications:** Quitting smoking can greatly benefit participant health. However, changes in smoking rate can lead to changes in how well some medications work.

Adequacy of Protection against Risk

Recruitment and informed consent. Potential subjects will be told the nature of the research over the phone or online during screening. They will be told they may discontinue participation at any time and will not be discriminated against if they choose to do so. Subjects will be told their participation in the project will be strictly confidential, that any identifying information will be available to the project investigators or institutional or federal regulatory groups only, and that no identifying information concerning the data and results will be made

known. Subjects will have written assurance that while de-identified individual subject data may be available to other researchers for research purposes, only a summary of the results will ever be published or otherwise publicly released. They will also be informed that all raw data will be coded with numbers and any form with identifying information (e.g., consent forms) will be kept in locked file cabinets. If subjects would like their information on vitals released to another party, they will be asked to sign a release form. Subjects will be required to demonstrate an understanding of the study purpose and procedures prior to signing the consent form. Consent form must be signed before the research is started. All participants will be provided with a paper copy of the consent and HIPAA documents, but consent signatures may be collected on paper or electronically. When consent is collected electronically, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap if captured electronically. The HIPAA form can be signed on paper or electronically. For the electronic process, all pages of the approved HIPAA document will be uploaded into REDCap, using a SCTR-developed template and procedures, for review by the participant. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Each participant will still receive a paper copy of the "Notice of Privacy Practices" and each signed HIPAA can be downloaded from REDCAp as a PDF. These procedures will be done on our research team's combination laptop/tablet, but no data will be stored on the laptop/tablet; all data will be stored securely in REDCap.

Protection against risks.

1) **Issues Related to Coercion**: The likelihood of this risk is low because the compensation is commensurate with the amount of time and effort required for this study. Participants will be compensated for their time at a rate that is commensurate with the time and effort required for this study ($10/hr during the screening session, $55/day during the hotel phase).
2) **Breach of Confidentiality:** The likelihood of breach of confidentiality is low as we will take precautions to minimize this risk. All data will be stored on a secure, password-protected server that is only available to research investigators.
3) **Risk of fire:** Participants will be advised not to smoke in bed or other unsafe areas.
4) **Smoking Cigarettes:** The study cigarettes have risks that are similar to conventional cigarettes, and all participants will be given information about smoking risks during the consent process and at the end of the study. Subjects will be encouraged to quit smoking and optimally all tobacco use at the end of study. We will perform a urine pregnancy test on female participants at the screening session and on the first day of each hotel week. Participants testing positive for pregnancy will be excluded (screening) or withdrawn (hotel phase). We will advice women to use proper birth control while enrolled in the study. Women who self-report using estrogen birth control will not be eligible to participate.
5) **Smoking Study Cigarettes:** Risks related to withdrawal are likely uncomfortable, but the risk is minimal. Although smoking the study cigarettes may result in increased smoking, we have observed in our prior studies that this increase is temporary, and smoking rates return to normal within 30 days after the study ends. This is true even for participants that experience large increases in smoke exposure during the study (>100% increase in CPD). We have established clear rules for monitoring and withdrawing participants (see Data and Safety Monitoring Plan). For example, participants would be withdrawn from the study if at any point, the average CO over two consecutive readings is greater than 99 ppm.

If the subject decides to quit smoking before completing the entire study, this decision will be encouraged and supported. Subjects will be provided with a treatment manual and referral to available treatments.

Potential Benefits of the Proposed Research to Human Subjects and Others

There are no direct benefits to the research participants. Referrals to community resources for quitting smoking will be made at the end of study participation. The risks compared to potential benefits are minimal to the individual research subject and virtually nonexistent to others or society in general.

Importance of Knowledge Gained

The benefit to society may be potentially significant if the end result from this study is to assess whether a reduction in nicotine content is likely to result in an increase in smoke exposure.

Data Safety Monitoring Plan

1. Summary of the Protocol

a. Brief Description

The Family Smoking Prevention and Tobacco Control Act (FSPTCA) gives the FDA the authority to reduce the nicotine content of cigarettes to any nonzero amount. A drastic reduction in the nicotine content of cigarettes may improve public health by resulting in a reduction in the prevalence of smoking. One of the primary concerns regarding a nicotine reduction strategy is that smokers will modify their smoking behavior to increase their nicotine delivery—resulting in an increase in exposure to cigarette smoke (i.e., compensation). While there is little evidence from clinical trials to suggest that smokers are likely to compensate, most participants in clinical trials use non-study normal nicotine content cigarettes, likely to supplement their nicotine intake. Thus, it remains unclear whether a reduction in nicotine content will result in compensatory smoking when access to normal nicotine content cigarettes is restricted, as would be the case following a nicotine reduction policy. The present study will assess whether a reduction in nicotine content will result in compensatory smoking when access to normal nicotine content cigarettes is restricted.

The Medical University of South Carolina will approve the study and all participants will sign informed consent prior to participation.

Participants will be recruited through newspaper, social media, bus, TV, radio and Craigslist advertisements. Thus, contact between participants and study staff will be initiated by the participants. Those who call into the laboratory will be read a script briefly explaining the study. After verbal informed consent is received the participants will be asked questions over the phone to determine initial eligibility. Alternatively, participants may complete a Redcap survey to determine initial eligibility. Participants will see a script that briefly explains the study. If eligible and interested, they will be scheduled for an in-person screening interview. Participants who are eligible and interested will be scheduled for an in-person screening session. Potential participants will be instructed to bring a pack of their usual brand cigarettes as well as all prescription medications they are currently taking to the screening visit.

During the in-person screening session, study information will be presented and written informed consent will be required to participate in the screening. The investigator will discuss the procedures, risks and benefits with the participant as well as their rights as a research participant. At the end of the presentation, the participants will be instructed to read several open-ended questions aloud and discuss the answers with the investigator. Only after the participant and the investigator are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data, the procedures, the risks/benefits and their rights as a research participant will the consent form be signed and the participant undergo screening procedures.

Copies of informed consent will be kept by research personnel under lock and key, or on recap when collected electronically. When consent is collected electronically, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap if captured electronically. The HIPAA form can be signed on paper or electronically. For the electronic process, all pages of the approved HIPAA document will be uploaded into REDCap, using a SCTR-developed template and procedures, for review by the participant. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Each participant will still receive a paper copy of the "Notice of Privacy Practices" and each signed HIPAA can be

downloaded from REDCAp as a PDF. These procedures will be done on our research team's combination laptop/tablet, but no data will be stored on the laptop/tablet; all data will be stored securely in REDCap.

b. Primary and Secondary Outcome Measures

The primary outcome for Aim 1 is expired carbon monoxide. The primary outcomes for Aim 2 will be average cigarettes smoked per day and total puff volume as assessed using puff topography. Other outcomes of interest include urinary cotinine, cigarette butt weight, the Minnesota Withdrawal Scale, the Questionnaire of Smoking Urges score, the Cigarette Evaluation Scale, the Cigarette Purchase Task, the Perceived Health Risks Questionnaire, the Fagerström Test for Nicotine Dependence, the Wisconsin Inventory of Smoking Dependence Motives, and the Smoking Consequences Questionnaire-Adult.

c. Inclusion/Exclusion Criteria

Inclusion criteria will include the following:

a) male or female participants who are at least 18 years old and have been smoking between five and thirty cigarettes daily for the past month (CO > 8, if CO ≤ 8 ppm, then Nic Alert test of 6), and
b) willing to stay in the hotel for two four-night stays during the prearranged dates.

Exclusionary criteria are designed to enroll relatively healthy smokers who are not interested in quitting smoking. They include:

j) interested in quitting smoking in the next month,
k) unwilling to use research cigarettes as part of the trial,
l) use of smokeless, hookah, cigars, e-cigarettes, or tobacco products besides cigarettes ≥ 10 days in the past 30,
m) Binge drinking ≥10 days in the past month, or reporting that it would be difficult to abstain from illicit drug use while in the hotel
n) self-reported illicit drug use ≥ 10 days in the past month or positive urine toxicology (positive toxicology screen for marijuana acceptable), or reporting that it would be difficult to abstain from illicit drug use while in the hotel
o) pregnant, trying to become pregnant, or breastfeeding,
p) currently using nicotine replacement therapies or other pharmacotherapies as a cessation aid,
q) current or recent (past month) suicidal ideation,
r) new diagnosis, difficulty with, or seeking medical attention for the following diagnoses in the last three months: heart attack, stroke, arteriosclerosis, heart disease, hypertension, emphysema, asthma, COPD, or cancer.

Children under age 18 are excluded because they cannot legally buy cigarettes. Those with unstable medical or medication conditions (condition and/or medication changes in the past 3 months) are excluded as these symptoms could affect a participant's ability to complete the study. We will exclude those currently seeking smoking treatment, as participation in this study may not lead to reductions in smoking. We will exclude pregnant and nursing women and anyone with current or recent alcohol or drug abuse problems as these factors could independently affect smoking behavior during the study.

d. Power Analysis and Sample Size

Our goal is to enroll 20 participants who complete the Hotel Phase. We may consent up to 50 participants because we expect that approximately 50% of participants will not be eligible to participate after screening, and that 10% may lose interest or withdraw prior to the hotel phase. We assume that 100% of participants who initiate the hotel phase will complete the study based on our prior hotel study which had a 100% completion

rate. Up to four additional participants will be recruited to serve as alternates during the hotel phase in case another eligible participant is unexpectedly unable to attend the hotel phase.

Primary outcomes for Aim 1 is expired carbon monoxide. Carbon Monoxide is expected to be skewed and will be log transformed. The primary outcomes for Aim 2 are cigarettes smoked per day and total puff volume. This study is powered to detect an increase in smoke exposure of 20%. Our effect size for this power analysis was taken from the existing literature on "light" cigarettes and the increase in smoke exposure produced for light cigarettes. For example, in a recent paper from Dr. Neal Benowitz's lab (2), switching to light cigarettes produced an increase in cigarettes smoked per day from 22.5 CPD to 27.5 CPD (22% increase). A predicted increase in exposure of 20% is conservative in that compensation for VLNC cigarettes, if present, is likely to be much larger than compensation for light cigarettes because the reduction in nicotine yield for VLNC cigarettes is much larger than the reduction in nicotine yield for light cigarettes.

2. Trial Management

a. List of Participating Enrollment Clinics or Data Collection Centers

Data will be collected at one site (Medical University of South Carolina, PI: Tracy T. Smith, Ph.D.).

b. Projected Timetable

We have conducted a similar study to this one in the past, and thus are familiar with the methods proposed here. We anticipate no issues in adhering to the proposed timeline. Recruitment and data collection will take place over the last half of Year 1 and first half of Year 2. The remaining portion of Year 2 will be used for data collection, data presentation, and manuscript preparation.

c. Target Population Distribution

We plan to enroll 50% men and 50% women. Expected percentages of racial and ethnic groups are 60% White, 30% Black or multiracial, 10% Asian, and 10% Hispanic.

3. Data Management and Analysis

a. Data Acquisition and Transmission

Research materials include questionnaires, expired air samples for analyzing carbon monoxide and breath alcohol levels, urine samples for analyzing nicotine exposure, and urine drug and pregnancy screens. Research data without identifiers will be maintained in a locked file cabinet and on password-protected computers in the research staff workplace, with only alpha-numeric codes identifying subjects. Study consent forms and the linkage between the participants' names and codes will be stored in a locked file cabinet in a separate location from the study data. All information collected as part of this study will be accessible only to research staff.

b. Data Entry Methods

Some interview and participant-administered questionnaires will be completed on paper. Those data will be entered by the Research Assistant shortly after completion of the assessment. Electronic entries will be verified against the source document by a second Research Assistant.

c. Data Analysis Plan

Data analysis will be completed by Dr. Tracy Smith.

The primary statistical analysis will use linear mixed model with fixed effects for nicotine content, period, and order, and random effects for subject and group. The type-1 error rate will be 0.05. Continuous outcomes will be summarized by the mean, standard deviation, median and range, while categorical outcomes will be summarized by frequencies and percentages. Skewed continuous outcomes will be log-transformed or square root-transformed as appropriate; for example we conventionally analyze cotinine on log scale.

Biomarkers will be analyzed in a natural log scale such that the model assumptions of normality and equal variances can hold, and geometric means in original units will be calculated as well. A p-value < 0.05 would be conventionally used as "statistical significance".

4. Quality Assurance

a. Procedures in place to ensure the validity and integrity of the data

It will be made clear to participants that all information obtained during assessments is confidential and that no information will be shared with the participants' clinicians unless the participant requests this in writing. All investigators and staff associated with this project have been trained, and new hires will be trained, on human research ethics in accordance with the requirements of the local institutions during initial project approval.

Dr. Tracy Smith will train and closely monitor the Research Assistants on the procedures to be used in this study. Such monitoring will consist of frequent in-person discussion of study visits at the beginning of the study and less frequent monitoring as the study progresses. The PI (Dr. Smith) will also be present during the Hotel Phase of the experiment, and will discuss any issues with research assistants at least daily.

The first time that participants complete the questionnaires, the Research Assistants will go over the questionnaires to ensure that participants understand the questions. Questionnaires will be reviewed for completeness while the participant is present. Other questionnaires are completed on the computer, so that participants cannot skip a question. Several biochemical measures (expired breath CO, urine pregnancy and drug screens) will be analyzed immediately, while the participant is present. If necessary (e.g., if the sample volume is insufficient for analysis), the Research Assistants can gather another sample immediately and re-analyze.

Data will be collected in a consistent manner across both Hotel Phases of the experiment. Standard operating procedures will be developed. Case report books will be made for to standardize recording. Each visit or Hotel Check In will have a checklist of all measures that need to be obtained and the order by which these measures are administered.

b. Data collection/entry/transmission/analysis

Many subjective measures will be administered via a data collection website, using electronic forms. These will be identified by Redcap Subject Identifier, which will be generated by Redcap, a participant tracking software system. Biological specimens will be marked with participant ID, transported to the Medical University of South Carolina laboratory suite daily. Smoking topography data will be collected using CReSS handheld topography devices. Data will be analyzed as outlined in Section 3.c. above.

5. Regulatory Issues

a. Reporting of SAEs to the IRB, NIDA and other regulatory authorities

Serious adverse events (SAEs) as defined in 21 CFR 312.32 (death, life-threatening event, new or prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, immediate medical or surgical intervention) will be reported in an expedited manner to NIDA's program office, and all applicable regulatory authorities in accordance with the Program's standard operating procedures. SAEs will be reported to the NIDA program official within 24 hours by phone, fax, and/or email and a written report will

also be submitted to the program official no more than two days later. SAEs that are deaths will be reported to the IRB in 24 hours. Unanticipated problems involving risks to subjects or others will be reported to the IRB within 10 working days after Dr. Smith is notified of the event.

b. Reporting Changes or Amendments to the Protocol

Any changes or amendments to the protocol made in response to adverse events/SAEs will be discussed with Tracy T. Smith, PhD, and then requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. NIDA will be informed of any approved changes in protocol by documentation in the noncompetitive continuation application. Changes that significantly alter the scope of the research or the ability of the research to achieve its specific aims will be submitted to NIDA for approval prior to implementation.

c. Trial Stopping Rules

The trial will be stopped if the local IRB recommends trial discontinuation due to SAEs, or if the trial is not progressing due to lack of participant recruitment.

6. Trial Safety

a *Potential Risks.*

Risks include breach of confidentiality, issues related to coercion, and risks related to smoking the study cigarettes.

6) **Issues Related to Coercion**: Coercion is a possible risk due to monetary compensation for participating in this study. The likelihood of this risk is low because the compensation is commensurate with the amount of time and effort required for this study, as described below under Adequacy of Protection against Risk in the Human Subjects Protection Plan.
7) **Survey Questionnaires:** This study will include questions about medical history, drug and alcohol use, and questionnaires about mood. Answering these personal questions could participants uncomfortable.
8) **Breach of Confidentiality:** Study data include biological measures of cigarette smoking, pregnancy and illicit drug use. The likelihood of breach of confidentiality is low as we will take precautions to minimize this risk as described below under Adequacy of Protection against Risk.

9) **Smoking Cigarettes:** All cigarettes are detrimental to a person's health and can lead to significant medical problems including:
    h. **Cardiovascular Diseases**: Coronary heart disease, heart attack, stroke, peripheral vascular disease, reduced blood circulation, abdominal aortic aneurysm
    i. **Respiratory Diseases**: Emphysema, bronchitis, and chronic airway obstruction
    j. **Cancers**: Cancers of the lung, bladder, cervix, esophagus, kidney, larynx, mouth, pancreas, throat, and stomach; leukemia
    k. **Other Health Risks Associated with Smoking**: Including but not limited to infertility, lower bone density in postmenopausal women, and hip fracture in women
    l. **Death**
10) **Smoking Study Cigarettes:** Smoking the study cigarettes could cause some minor adverse health effects such as headaches or experience withdrawal symptoms, which are listed below. Due to the altered nicotine levels, there could be a change in cigarette use including the manner in which smoke is inhaled. Participants may also experience increases in levels of carbon monoxide, a gas from smoke.
11) **Smoking Withdrawal:** Participants may experience smoking withdrawal symptoms during this study. These symptoms can include anger, irritability, frustration, anxiousness, nervousness, depressed mood or sadness, desire or craving to smoke, difficulty concentrating, increased appetite, hunger or weight gain, insomnia, problems sleeping or awakening at night, restlessness, impatience, constipation, dizziness, coughing, dreaming or nightmares, nausea, and sore throat. These feelings can be uncomfortable but are typically of minimal risk.

12) **Returning to Regular Smoking**: It is possible that if when participants return to smoking their usual brand of cigarette they may experience mild and transient nausea, dizziness, and lightheadedness.
13) **Risk to Fetus:** Smoking during pregnancy can lead to miscarriage, preterm delivery, stillbirth, low birth weight, problems with the placenta, birth defects such as cleft palate, sudden infant death syndrome (SIDS), and early childhood behavioral problems.
14) **Changes in blood pressure and/or heart rate:** Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate.
15) **Changes in mood, emotions and psychiatric symptoms**: Smoking and nicotine can affect mood and emotions and are associated with psychiatric disorders including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or cigarette consumption could adversely affect mood, emotions and the symptoms related to psychiatric conditions in some individuals.
16) **Smoking and oral contraceptives in women:** Women who smoke and are over the age of 35 should not take oral contraceptives that contain estrogen without consulting their physician.
17) **Smoking and medications:** Quitting smoking can greatly benefit participant health. However, changes in smoking can lead to changes in how well some medications work.
18) **Risk of fire:** Smoking cigarettes inside an enclosed structure (e.g. house, apartment, hotel room) can increase the chances of starting a structural fire. To reduce this risk, participants will be instructed avoid smoking under conditions that might increase the chance of starting a fire (e.g. in bed).

b *Direct Benefits:* There are no immediate benefits from participating in the study. The information obtained from this study may ultimately help the Food and Drug Administration decide how best to regulate tobacco products with the goal of improving public health.

C. Monitoring and Withdrawal of Participants

<u>Identifying Adverse Events</u>

While participating in the trial, adverse events and concomitant medications will be assessed at every lab visit and at the end of the Hotel Phase, and expired carbon monoxide will be obtained. Adverse events will typically be identified during the administration of the Health Changes Questionnaire, which will be administered at the end of the Hotel Phase,. Other events may be identified from physiological study measures or by spontaneous reports during non-scheduled assessments. Dr. Carpenter (CO-I) has worked closely with Dr. Kevin Gray (MD) in handling Adverse Events in the past, and Dr. Gray has agreed to be available as needed to discuss adverse events in this study.

Questionnaire items that will be reviewed:

- <u>Health Changes Questionnaire</u>: If the participant answers **'YES'** to **Questions 1** , the interviewer should administer the 'Adverse Event Form.' The Adverse Event form will ask for additional details about changes in physical and mental health.
    1) ***Have you had any negative changes in your physical or mental health that you think might be related to study participation?***

Physiological data that will be reviewed:

- <u>CO level</u>: The 'Adverse Event Form' should be completed if the average CO within any visit or Hotel Check in is:
    - CO is greater than 50 ppm if CO at Screening is < 20 ppm.
    - CO is greater than 60 ppm if CO at Screening is 20 – 34 ppm.
    - CO is greater than 70 ppm if CO at Screening is 35 – 49 ppm.
    - CO is greater than 80 ppm if CO at Screening is 50 – 64 ppm.
    - CO is greater than 90 ppm if CO at Screening is 65 – 80 ppm.

Participants will be withdrawn immediate if any of the following occur:

1. 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., mitrial or aortic regurgitation).
2. If they are required to leave the hotel for any reason (e.g., personal, medical)
3. Change in medical or psychiatric status: If a change in medical or psychiatric status as determined by the PI may present previously unrecognized risk to study staff, hotel staff, other participant or self.
4. DVT/PE: deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system
5. Suicide Attempt or Ideation: A participant will be withdrawn if he/she attempts suicide or expresses any suicidal ideation at any time during participation in the study.
6. Pregnancy: If a participant indicates she is pregnant, she will be withdrawn from the study, and this event will remain open until delivery. At that time study staff will contact the participant to ask a few questions about the baby's health and will update the open "Adverse Event Form"
7. Expired breath carbon monoxide increase: A participant will be withdrawn from the study if the average of two consecutive readings during the same visit is 100 ppm or greater.

The following will be monitored and could lead to the participant being withdrawn:

1. Expired Carbon monoxide increase: If a participant's CO is
    a. Greater than 50 ppm for participants with CO of less than 20 ppm at Screening
    b. Greater than 60 ppm for participants with CO of 20-34 at Screening
    c. Greater than 70 ppm for participants with a CO of 35-49 at Screening
    d. Greater than 80 ppm for participants with a CO of 50-64 at Screening
    e. Greater than 90 ppm for participants with a CO of 65-80 at Screening
    Another CO reading will be taken after 10 minutes have passed. If the reading is still out of range, a Adverse Event Form will be completed.
2. Any injury that occurs during the hotel phase could result in study discontinuation.
3. If a participant is behaving in an inappropriate or threatening manner, is disruptive to research and hotel staff, admits to lying about eligibility criteria, is smoking non-Spectrum cigarettes while at the hotel, is using any non-cigarette tobacco product while at the hotel, leaves the hotel, breaks curfew or has visitors, the PI can withdraw him/her from the study at the PI's discretion.

Management of SAEs and Other Study Risks

When an AE occurs, study staff will review the AE with Dr. Smith within 24 hours. A study participant may be discontinued from the study if the PI determine it is the best decision in order to protect the safety of a participant. Dr. Carpenter (CO-I) has worked closely with Dr. Kevin Gray (MD) in handling Adverse Events in the past, and Dr. Gray has agreed to be available as needed to discuss adverse events in this study. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to an AE/SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing an AE/SAE will be followed until the problem resolves, stabilizes, or is clearly unrelated to the study cigarettes.

Reporting of SAEs to the IRB, FDA, and NIDA

Serious adverse events (SAEs) as defined in 21 CFR 312.32 (death, life-threatening event, new or prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, immediate medical or surgical intervention) will be reported in an expedited manner to NIDA's program office, and all applicable regulatory authorities in accordance with the Program's standard operating procedures. SAEs will be reported to the NIDA program official within 24 hours by phone, fax, and/or email and a written report will also be submitted to the program official no more than two days later. SAEs that are deaths will be reported to

the IRB in 24 hours. Unanticipated problems involving risks to subjects or others will be reported to the IRB within 10 working days after Dr. Smith is notified of the event.

Reporting of IRB Actions to NIDA

Actions taken by the local IRBs in response to SAEs will be reported to NIDA in the annual noncompetitive continuation application, as will reports of changes or amendments to the protocol as a result of an SAE. Recommendation for trial discontinuation, for significant changes or amendments to the protocol, or other significant findings as a result of an SAE will be reported immediately to the NIDA Scientific and Project Officer by the Project PI.

Reporting Changes or Amendments to the Protocol

Any changes or amendments to the protocol made in response to adverse events/SAEs will be requested in writing to the IRB, which will then grant or deny permission to make the requested change in protocol. The DSMB and FDA will be notified about any significant changes to the protocol. NIDA will be informed of any approved changes in protocol by documentation in the noncompetitive continuation application. Changes that significantly alter the scope of the research or the ability of the research to achieve its specific aims will be submitted to FDA and NIDA for approval prior to implementation.

7. Trial Efficacy

a. Plans for interim analysis of efficacy data

Interim analyses will not be conducted because the proposed study is not an efficacy trial.

8. DSM Plan Administration

a. Responsibility for data and safety monitoring

The Principal Leader (Dr. Tracy Smith) will be responsible for monitoring the safety and efficacy of this trial, executing the DSM plan for this project and complying with the reporting requirements. The PI will provide an annual summary of the DSM report along with the progress report.

b. Frequency of DSM reviews

Dr. Smith will review the safety data in real time. The staff will contact her about any SAE or event that meets the criteria for monitoring or withdrawing a participant. She will also conduct a review of all safety data at the end of each day during the Hotel Phase of the experiment including the Health Changes Questionnaire, carbon monoxide measures, and session notes provided by research staff.

c. Content of DSM report

The DSM report will include the demographics of the participants, the expected versus actual recruitment rates, quality assurance or regulatory issues that may have occurred during the year, a summary of reportable events and SAEs and any actions or changes to the protocol. Also included will be any and all actions by the IRBs.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Impact of exclusive use of low nicotine cigarettes on compensatory smoking

Total Planned Enrollment: 50

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	23	23	46
Ethnic Category: Total of All Subjects *	25	25	50
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	1	1	2
Black or African American	7	7	14
White	14	14	28
Racial Categories: Total of All Subjects *	25	25	50

*** The ethnic Category: "Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."**

FACILITIES AND RESOURCES

Medical University of South Carolina

MUSC has a substantial research enterprise with 1242 extramural awards totaling more than $232 million in FY2012. The Chronicle of Higher Education's 2011-12 Almanac Issue recognized MUSC as one of the top 10 institutions with the "biggest gains in federal funds for research and development in science and engineering, adjusted for inflation, 1999-2009". Federal funding constitutes about 67% of extramural support, with the National Institutes of Health as the primary funding agency. MUSC's ranking in R&D expenditures at universities and colleges increased from 94th in FY08 to 87th in FY09 [NSF 11-313, July 2011].

The South Carolina SmartState™ Program was created by the South Carolina legislature in 2002 and is funded through South Carolina Education Lottery proceeds. The legislation authorizes the state's three public research institutions, Medical University of South Carolina, Clemson University and the University of South Carolina, to use state funds to create Centers of Economic Excellence in research areas that will advance South Carolina's economy. To date, 49 Centers have been created and 38 SmartState Endowed Chairs have been appointed to lead the centers. The SmartState Program has resulted in more than $400 million dollars in non-state investment into the South Carolina economy and is responsible for the creation of 5,000 jobs.

To date, this has resulted in initiating 19 SmartState™ Centers at MUSC, bringing the total of MUSC endowed chairs and named professorships to 41 (20 appointed as of January 2013). The Department of Pediatrics is currently recruiting for one of these endowed chairs for a basic researcher in pediatric neurodegenerative diseases. In addition to the obvious benefit of providing substantial resources to recruit senior research leadership and entrepreneurship, the program has dramatically raised the profile of university-based research in South Carolina – especially biomedical and clinical/translational research – and stimulated significant philanthropy to meet match requirements. For FY 2012, the Medical University received more than $76.7 million in new gifts, pledges and pledge payments.

Elsewhere on campus, the SC Clinical and Translational Research Institute (SCTR) is one of NIH's Clinical and Translational Science Award Programs. SCTR's Society of Clinical Research and Translational Early Scientists, a mentoring forum for all faculty members, holds monthly meetings where Early Stage Investigators present their research proposals and get feedback. Other SCTR resources include: 1) extensive research support, including biostatistical assistance, database management, and a clinical data warehouse; 2) a robust Pilot Project Program that awards more than $1 million in seed funds for promising multi-disciplinary research; and 3) a voucher program whereby investigators may request funds to pay for lab services, participant recruitment, ethics consultations, and other research costs.

Department of Psychiatry

The Department of Psychiatry and Behavioral Sciences (Dr. Carpenter's academic department) **ranks 7th among psychiatry departments in the U.S in NIH FY12 funding**. In the most recently completed fiscal year (June 30, 2012) departmental faculty received 173 grant and contract awards, totaling $40.8 million in extramural research support. For 2012, *U.S. News and World Report* ranked MUSC as #9 in the country among Best Medical Schools for Drug and Alcohol Abuse Programs. Within the Department, the Division of Clinical Neuroscience (Dr. Carpenter's division) has the highest NIH funding per faculty across any program on campus. To promote interdisciplinary interaction and collaboration among addiction researchers, the Department supports a Tobacco Research Retreat and Addictions Research Retreat on an annual basis, both of which involve presentations by nationally and internationally renowned experts. The Department's Center for Drug and Alcohol Programs (CDAP) provides evidence-based treatment for drug abuse and dependence and advances knowledge through high quality basic, clinical, and translational research.

Within the Department of Psychiatry, the **Clinical Neurobiology Laboratory (CNL)** is a fully equipped clinical and research laboratory, comprised of two 450 square foot laboratories on the first floor of the IOP North, and a phlebotomy area on the first floor hallway adjacent to the lab. Since its inception 20 years ago, the laboratory has been certified by the College of American Pathology (CAP) and compliant with the Clinical Laboratory Improvement Act (CLIA) as well as the Joint Commission, utilizing extensive quality control and proficiency testing programs. The laboratory performs analyses of urine samples for tests used for research and the clinical care of patients, and will perform nicotine/cotinine analyses for the current study.

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