Abuse Liability of Reduced Nicotine Cigarettes Experiments 1 and 2

ClinicalTrials.gov ID: NCT02951143

November 4, 2019

VirginiaTech

Institutional Review Board
Research Protocol

Once complete, upload this form as a Word document to the IRB Protocol Management System: https://secure.research.vt.edu/irb

Section 1: General Information

1.1 DO ANY OF THE INVESTIGATORS OF THIS PROJECT HAVE A REPORTABLE CONFLICT OF INTEREST? (http://www.irb.vt.edu/pages/researchers.htm#conflict)

☒ ***No***
☐ ***Yes,*** explain:

1.2 WILL THIS RESEARCH INVOLVE COLLABORATION WITH ANOTHER INSTITUTION?

☐ ***No,*** go to question 1.3
☒ ***Yes,*** answer questions within table →

IF YES
Provide the name of the institution [for institutions located overseas, please also provide name of country]***:*** **Carilion Hospital**
Indicate the status of this research project with the other institution's IRB: ☐ Pending approval ☐ Approved ☐ Other institution does not have a human subject protections review board ☒ Other, explain: **Human subject activities covered in this protocol.**
Will the collaborating institution(s) be engaged in the research? (http://www.hhs.gov/ohrp/policy/engage08.html) ☒ No ☐ Yes
Will Virginia Tech's IRB review all human subject research activities involved with this project? ☐ No, provide the name of the primary institution: ☒ Yes *Note: primary institution = primary recipient of the grant or main coordinating center*

1.3 IS THIS RESEARCH FUNDED?

☐ ***No,*** go to question 1.4
☒ ***Yes,*** answer questions within table →

IF YES
Provide the name of the sponsor [if NIH, specify department]: **NIH/National Institute on Drug Abuse**
Is this project receiving federal funds? ☐ No ☒ Yes ***If yes,***

Does the grant application, OSP proposal, or "statement of work" related to this project include activities involving human subjects that are <u>not</u> covered within this IRB application?

☒ No, all human subject activities are covered in this IRB application
☐ Yes, however these activities will be covered in future VT IRB applications, these activities include:
☐ Yes, however these activities have been covered in past VT IRB applications, the IRB number(s) are as follows:
☐ Yes, however these activities have been or will be reviewed by another institution's IRB, the name of this institution is as follows:
☐ Other, explain:

***Is* Virginia Tech the primary awardee or the coordinating center of this grant?**

☐ No, provide the name of the primary institution:
☒ Yes

1.4 DOES THIS STUDY INVOLVE CONFIDENTIAL OR PROPRIETARY INFORMATION (OTHER THAN HUMAN SUBJECT CONFIDENTIAL INFORMATION), OR INFORMATION RESTRICTED FOR NATIONAL SECURITY OR OTHER REASONS BY A U.S. GOVERNMENT AGENCY?

For example – government / industry proprietary or confidential trade secret information

☒ ***No***
☐ ***Yes,*** describe:

1.5 DOES THIS STUDY INVOLVE SHIPPING ANY TANGIBLE ITEM, BIOLOGICAL OR SELECT AGENT OUTSIDE THE U.S?

☒ ***No***
☐ ***Yes***

Section 2: Justification

2.1 DESCRIBE THE BACKGROUND, PURPOSE, AND ANTICIPATED FINDINGS OF THIS STUDY:

Abuse liability of reduced nicotine content cigarettes: Experiment 1
IRB
v.8
03/15/2019

With the recently acquired mandate of the FDA to regulate the rapidly increasing market of tobacco products, research that can inform these regulations is vital. Before modifying the tobacco product marketplace through regulatory action, it is important to understand how specific features of tobacco products influence the choices to purchase and consume that product. The long-term goal of this line of research is to build an evaluative framework to assess how different aspects of tobacco products that may be subject to regulatory action (e.g., flavor, nicotine content, packaging) influence decisions to purchase and consume those products across a range of prices. To craft effective regulations, it is important to understand how specific features of tobacco products that may be subject to regulatory action influence the choice to purchase and consume that product.

Economic demand analyses quantify the relationship between the cost of a commodity and population-level measures of consumption of that commodity. Behavioral economic demand analyses are analogous to these population-level analyses, but can be used to understand the level of motivation to consume a product on either an individual or small group level, including cigarettes (Bickel et al., 1995; MacKillop et al., 2008). This level of analysis allows for experimental manipulations to be made on variables of interest. By quantifying how consumption decreases as costs to obtain and consume a product increase, important indices of demand are obtained. These indices can be grouped into two main measures of consumption,

demand intensity and demand elasticity, which are associated with use level and dependence severity (MacKillop et al., 2008, 2009, 2010; Murphy et al., 2011). Demand intensity is the amount of the commodity consumed when available at a very low cost approaching free, and demand elasticity quantifies the degree to which the individual is willing to increase monetary or effort-based expenditures to maintain the same level of consumption as costs increase. Elasticity of demand has been shown to be a characteristic of the drug itself and independent of drug dose for many drugs including nicotine (Bickel et al., 1991; Hursh & Roma, 2013; Hursh & Silberberg, 2008; Hursh & Winger, 1995).

While drug demand plotted as a function of unit price has been often shown to be a function of the total drug consumed, there is some research with cigarette demand that call this finding into question. The most prominent of these is a study by Johnson et al. (2004) that compared conventional cigarettes to denicotinized cigarettes. They found that, if they were the only tobacco product available, the denicotinized cigarettes had comparable demand to nicotinized cigarettes. If both were available, participants preferred the nicotinized cigarettes. This suggests that cigarette demand is not strictly regulated by nicotine dose, and that there is substantial abuse liability associated with the cigarettes themselves apart from any nicotine content.

The specific objective in the proposed research is to examine the effect of nicotine content (0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, and 17.4 mg/g of tobacco) and blood nicotine absorption on laboratory behavioral economic measures of demand intensity and elasticity. Under double-blind conditions, we will examine the relationship between plasma nicotine and cigarette demand as a function of the dose of the nicotine in the cigarettes. Regular cigarette smokers will consume, on separate sessions, controlled puffs of a cigarette containing a blinded dose of nicotine then complete a cigarette purchase task, our measure of value, while plasma nicotine is measured. We hypothesize that cigarette demand will be associated with dose and level of circulating nicotine, but in a nonlinear fashion such that consumption of very low dose cigarettes will not be predicted by nicotine dose or intake alone.

2.2 EXPLAIN WHAT THE RESEARCH TEAM PLANS TO DO WITH THE STUDY RESULTS:

For example - publish or use for dissertation

The research team intends to publish the results of the current study in peer-reviewed journals.

Section 3: Recruitment

3.1 DESCRIBE THE SUBJECT POOL, INCLUDING INCLUSION AND EXCLUSION CRITERIA AND NUMBER OF SUBJECTS:

Examples of inclusion/exclusion criteria - gender, age, health status, ethnicity

Up to 250 current cigarette smokers will be recruited from the community surrounding Roanoke, VA. Eligible participants will be 18 to 65 years old, smoke at least 5 cigarettes per day, have a breath carbon monoxide (CO) level of at least 10 ppm at intake, and have no immediate plans to quit smoking. Females who are planning pregnancy, pregnant, lactating, not willing to use contraception during the study, and individuals who weigh less than 110 lbs or who have plans to move out of the area during the course of the experiment will be excluded from participation. Use of other tobacco/nicotine products will not be exclusionary. These minimally restrictive inclusion/exclusion criteria will allow for a broad range of participants and increase the generalizability to tobacco regulation of our eventual results. Individuals who do not meet these eligibility criteria may be rescreened to see if they are eligible after at least 30 days has passed.

3.2 WILL EXISTING RECORDS BE USED TO IDENTIFY AND CONTACT / RECRUIT SUBJECTS?

Examples of existing records - directories, class roster, university records, educational records

☐ ***No,*** go to question 3.3
☒ ***Yes,*** answer questions within table →

IF YES

Are these records private or public?

☐ Public

☒ Private, describe the researcher's privilege to the records: **Participants will be contacted if they have given prior permission (through a previous informed consent form) or by completion of a confidential pre-screening questionnaire.**

Will student, faculty, and/or staff records or contact information be requested from the University?

☒ No

☐ Yes, visit the following link for further information: http://www.policies.vt.edu/index.php (policy no. 2010)

3.3 DESCRIBE RECRUITMENT METHODS, INCLUDING HOW THE STUDY WILL BE ADVERTISED OR INTRODUCED TO SUBJECTS:

Participants will be recruited from the community via advertisements such as posted flyers, internet (e.g., Facebook or other websites), etc. To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers may be addressed by providing transportation or parking costs for participants, and scheduling barriers will be minimized by offering a flexible study visit schedule. Compensation may be provided for travel costs and time. All methods and measures will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with online human subjects training. We have a history of successful recruitment of cigarette smokers into research programs. All participants will enroll on a voluntary basis.

3.4 PROVIDE AN EXPLANATION FOR CHOOSING THIS POPULATION:

Note: the IRB must ensure that the risks and benefits of participating in a study are distributed equitably among the general population and that a specific population is not targeted because of ease of recruitment.

Cigarette smokers will be recruited for this study. This population was chosen because the current experiment entails smoking cigarettes. Non-smokers would not be appropriate because nicotine and tobacco smoke may make individuals that do not regularly smoke feel ill. Otherwise healthy individuals are sought to minimize any ill effects that exposure to nicotine and cigarette smoke may cause.

Section 4: Consent Process

For more information about consent process and consent forms visit the following link: http://www.irb.vt.edu/pages/consent.htm

If feasible, researchers are advised and may be required to obtain signed consent from each participant unless obtaining signatures leads to an increase of risk (e.g., the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting in a breach of confidentiality). Signed consent is typically not required for low risk questionnaires (consent is implied) unless audio/video recording or an in-person interview is involved. If researchers will not be obtaining signed consent, participants must, in most cases, be supplied with consent information in a different format (e.g., in recruitment document, at the beginning of survey instrument, read to participant over the phone, information sheet physically or verbally provided to participant).

4.1 CHECK ALL OF THE FOLLOWING THAT APPLY TO THIS STUDY'S CONSENT PROCESS:

☐ Verbal consent will be obtained from participants

☒ Written/signed consent will be obtained from participants

☐ Consent will be implied from the return of completed questionnaire. Note: The IRB recommends providing consent information in a recruitment document or at the beginning of the questionnaire (if the study only involves implied consent, skip to Section 5 below)

☐ Other, describe:

4.2 PROVIDE A GENERAL DESCRIPTION OF THE PROCESS THE RESEARCH TEAM WILL USE TO OBTAIN AND MAINTAIN INFORMED CONSENT:

Potential participants will be provided with the written consent form prior to visiting FBRI at VTC (e.g., by email), if they wish. They will also be given additional time in a quiet room at FBRI at VTC to read the form. FBRI at VTC research staff will review each element of the written consent form with the potential participant. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. They will be encouraged to speak with whomever they wish before making this decision. Staff will reiterate that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence. The potential participant and person obtaining consent will sign the consent form after the potential participant verbally states that s/he understands the conditions of the study, has no more questions, and chooses to participate.

4.3 WHO, FROM THE RESEARCH TEAM, WILL BE OVERSEEING THE PROCESS AND OBTAINING CONSENT FROM SUBJECTS?

Study team members that have been delegated this responsibility by the PI.

4.4 WHERE WILL THE CONSENT PROCESS TAKE PLACE?

In a quiet room at the FBRI at VTC.

4.5 DURING WHAT POINT IN THE STUDY PROCESS WILL CONSENTING OCCUR?

Note: unless waived by the IRB, participants must be consented before completing any study procedure, including screening questionnaires.

Consenting will occur prior to any study procedures.

4.6 IF APPLICABLE, DESCRIBE HOW THE RESEARCHERS WILL GIVE SUBJECTS AMPLE TIME TO REVIEW THE CONSENT DOCUMENT BEFORE SIGNING:

Note: typically applicable for complex studies, studies involving more than one session, or studies involving more of a risk to subjects.

Prior to visiting the lab, participants will be given the option to reveive a copy of the consent form before attending a consent session. They will be able to receive the consent copy via e-mail, mail, or in person if they wish. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. They will be encouraged to speak with whomever they wish before making this decision.

☐ Not applicable

Section 5: Procedures

5.1 PROVIDE A STEP-BY-STEP THOROUGH EXPLANATION OF ALL STUDY PROCEDURES EXPECTED FROM STUDY PARTICIPANTS, INCLUDING TIME COMMITMENT & LOCATION:

We will first ask potential participants a series of brief screening questions to determine whether they will likely meet eligibility criteria. Individuals who are eligible based on the screening questionnaire will be scheduled for an informed consent session.

The current study will take place over approximately 10 laboratory sessions at the FBRI at VTC's Addiction Recovery Research Center including the consent session (approximately 1 hour). Following informed consent, participants may also be asked to leave a baseline CO sample and urine sample (females only). The urine sample will be tested for pregnancy in females. Weight will also be measured. We have included three screening questions that ask about intentions to quit and desire to seek treatment. If a participant reports discordant answers on the intentions to quit or seek treatment questions (e.g., indicates no plans to quit but expresses an interest in treatment), we will ask a clarifying question that more directly assesses our stated exclusionary criteria of an immediate plan to quit smoking. For these participants, a question will appear that asks: "You expressed some interest in either quitting smoking or smoking cessation treatment. Do you

have plans for a quit attempt in the next 30 days?" If the participant answers that s/he plans to quit, s/he will be excluded from participating in the 7 cigarette purchase sessions and provided the 1-800-QUITNOW (1-800-784-8669) hotline, which can connect callers to a variety of local resources for quitting. However, the participant will be allowed to complete the 7 cigarette purchase sessions if there are no plans to quit in the next 30 days. All participants will complete the assessment session (described below) and only participants who meet all eligibility criteria will go on to complete the 7 cigarette purchase sessions, each at least two days apart. There will be at most two cigarette purchase sessions per week.

Although we only anticipate that a participant's total commitment will not be longer than 5 weeks (2 purchase sessions/week [4 weeks] + 1 assessment session [1 week or less]), if more than 7 sessions are required (due to factors outside of the control of participants, for example, a participant is eligible to start a purchase session but blood is unable to successfully be drawn), at the beginning of the first session of the 6th week (6 weeks from the initial assessment session) we will obtain a urine sample (for females only) to verify the participant is not pregnant. This is to minimize the risk of the investigational tobacco product under study. If the female participant tests positive for pregnancy, she will be withdrawn from the study. Following withdrawal, we will follow-up with the participant (via phone call) until the outcome of the pregnancy is established.

One Assessment session (approximately 1 hour). The first lab session will be the assessment session to collect information from participants on substance use patterns and severity, as well as the results of behavioral and cognitive tasks that we think may inform or compliment the results from the main study (see appendix for examples). This may be on the same day as the consent session and all participants who provide informed consent will complete this session. Participants who are not eligible to continue (e.g., report immediate plans to quit) will not continue to complete the following 7 cigarette purchase sessions.

Seven Cigarette purchase sessions (approximately 1.5 hours). In the remaining seven cigarette purchase sessions (may be more than 7 due to factors outside of the control of participants, for example, a participant is eligible to start a purchase session but blood is unable to successfully be drawn), we will assess the behavioral economic demand intensity and elasticity of cigarettes with different nicotine concentrations. During each of these 7 cigarette purchase sessions, participants will consume either their usual brand of cigarette, an experimental cigarette containing 0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, or 17.4 mg/g nicotine, or a nonusual brand, commercially available cigarette. All but the nonusual brand, commercially available cigarettes will be presented in a randomized order across participants to control for any order effects; the nonusual brand, commercially available cigarette will be administered during the 7th session. The participants' preferred brand of conventional cigarettes will be used for the appropriate session. The cigarette doses will be blinded so the participants are not aware of the dose they will administer, leaving only subjective effects. Participants will be asked to abstain from consuming nicotine for 12 hours prior to each cigarette purchase session. Abstinence will be verified with breath CO at the beginning of the session, which will need to be <8 ppm to participate. If participants do not meet this criterion, they will be allowed to reschedule the session and try again. After repeated failed attempts, participant participation may be terminated. Each purchase session will begin with baseline ratings of nicotine craving, current drug effect, breath CO, and nicotine withdrawal symptoms. The baseline blood draw will also be collected at this time. Blood will be drawn with a catheter throughout the session by a registered nurse or other personnel with phlebotomist training to measure plasma nicotine levels during the sessions. The catheter will be removed at the end of each purchase session. Snacks and/or beverages will be available for the participants to consume, at their own discretion, should they begin to feel light-headed.

Five minutes into the session, participants will consume the cigarette randomly chosen for that session. Consumption will be modeled after the initial consumption period of Vansickel and Eissenberg (2013) and will consist of 10 puffs with each puff initiated 30 seconds after the previous. Consumption will occur in ventilated booths located in the Addiction Recovery Research Center specifically designed for this purpose.

To measure how the subjective effects and plasma nicotine levels dissipate over the course of an hour, visual analogue scales (VAS) ratings, breath CO, and 7 blood draws (3 mL each), including the baseline one, will be collected throughout the session (baseline and at minutes 10, 15, 20, 30, 45, and 60). The catheter will be flushed with saline (1 mL) after each draw, followed by a 1 mL discard draw to remove the saline flush. No heparin will be used. The 3 mL blood drawn per draw would result in 21 mL total blood per session and 126 mL total over the six cigarette purchase sessions. To maintain sterility, the site is covered with a Tegaderm, the port is cleansed with alcohol, and the staff handle the IV site with clean, gloved hands. After the VAS ratings at one of the timepoints, participants will complete hypothetical purchase tasks for the product they just consumed and some brief discounting tasks, similar to the ones completed during the

assessment session. The value of the nicotine product just consumed will be assessed by asking how many cigarette puffs the participant would purchase if they were available at different prices. Hypothetical purchase tasks are typically used to measure the consumption of a product already familiar to the participant. In this project, we will use this procedure in a novel way by asking participants to indicate their consumption decisions for a product they just consumed, but remain blinded to the nicotine content. This will prevent their responses being biased by preconceptions of dose information, instead tying purchasing behavior to the experienced effects of each dose.

Blood samples will be de-identified (i.e., only labeled with an arbitrary ID) and brought to or sent for testing to a laboratory that offers such services (e.g., LabCorp or Solstas at Carilion). Blood samples will only be tested for nicotine and the primary metabolite of nicotine (cotinine), after which they will be destroyed. In the event a researcher or other staff person is improperly exposed to a participant's blood, it will be tested for the presence of HIV, the Hepatitis B Virus, and the Hepatitis C Virus. The research team will follow proper procedures for testing and reporting as outlined by Virginia State Law, which includes sending the sample to a certified laboratory. Should a participant's blood require testing, s/he will be informed of the test results and provided with the opportunity to receive appropriate and timely counseling. In addition, the results will be sent to the local health department.

One Cigarette Comparison session (approx. 1.5 hours). After completing all blood draw sessions, participants may come back for one final in-lab session. No blood will be taken during this session. Participants will be provided an array of cigarettes consumed during the previous blood draw sessions. Cigarettes will be labeled with an arbitrary code (e.g., A, B, C) and participants may be told which of the blood draw sessions they consumed each cigarette. In the ventilated smoking booth, participants will take one to two puffs of each cigarette. Immediately after puffing the cigarette, participants will complete the tasks similar to those completed during the blood draw sessions (e.g., VAS ratings, hypothetical purchase tasks). Participants will take the one to two puffs approximately every 10 minutes and will be provided water or another bland beverage to cleanse the palate between puffs. After experiencing all cigarettes, participants will rank order the cigarettes (1-X [X being the number of cigarettes in the array] with 1 being the most preferred). Participants will also answer questions that directly compare each of the cigarettes (e.g., Assuming all of the cigarettes you just tried were available for you to purchase, would you pay to purchase and consume or would you pay to avoid and not consume this specific cigarette? And depending on their answer, What is the most you would pay to smoke 1 of these cigarettes OR What is the most you pay to avoid smoking 1 of these cigarettes).

5.2 DESCRIBE HOW DATA WILL BE COLLECTED AND RECORDED:

All data will be collected and recorded with custom-built computer programs and/or standardized paper forms by trained study staff.

5.3 DOES THE PROJECT INVOLVE ONLINE RESEARCH ACTIVITES (INCLUDES ENROLLMENT, RECRUITMENT, SURVEYS)?

View the "Policy for Online Research Data Collection Activities Involving Human Subjects" at *http://www.irb.vt.edu/documents/onlinepolicy.pdf*

☐ ***No,*** go to question 6.1
☒ ***Yes,*** answer questions within table

IF YES
Identify the service / program that will be used:
☐ www.survey.vt.edu, go to question 6.1
☐ Blackboard, go to question 6.1
☐ Center for Survey Research, go to question 6.1
☒ Other
IF OTHER:
Name of service / program: **REDCap, Craigslist, Facebook, Qualtrics**
URL: **http://www.redcap.com/ , https://www.craigslist.org/, https://www.facebook.com/, https://virginiatech.qualtrics.com**

This service is…

☒ Included on the list found at: http://www.irb.vt.edu/pages/validated.htm
☐ Approved by VT IT Security
☒ An external service with proper SSL or similar encryption (https://) on the login (if applicable) and all other data collection pages.
☐ None of the above (note: only permissible if this is a collaborative project in which VT individuals are only responsible for data analysis, consulting, or recruitment)

Section 6: Risks and Benefits

6.1 WHAT ARE THE POTENTIAL RISKS (E.G., EMOTIONAL, PHYSICAL, SOCIAL, LEGAL, ECONOMIC, OR DIGNITY) TO STUDY PARTICIPANTS?

One risk of participation is embarrassment that may come from answering sensitive questions related to medical, psychiatric, and/or drug use history. Loss of confidentiality is another risk of participation. Participants may also experience discomfort during the blood draw sessions.

6.2 EXPLAIN THE STUDY'S EFFORTS TO REDUCE POTENTIAL RISKS TO SUBJECTS:

Participants will be screened, using medical history and structured interviews, for a history of medical contraindications (e.g., pregnancy), and current unstable medical illnesses. The study will occur in our facilities at the FBRI at VTC. Participants will be free to withdraw from the study at any time, and their refusal to continue will not affect other medical care associated with Carilion. Participants who become pregnant during the course of the study will be withdrawn. Following withdrawal, these participants will be followed up (via phone) to determine the outcome of the pregnancy (e.g., were there any complications?). In addition, if participants develop medical problems or experience adverse events during the course of the study, assessments to determine whether participants should continue in the study and/or continue to use study products will be conducted and necessary referrals will be provided. Using only ID numbers and keeping all data in secure locations and/or in locked offices accessible only to trained study team members will protect confidentiality. Computer databases will have coded identifiers. These screening, monitoring, and confidentiality procedures have been in effect for more than 10 years and for more than 2,000 subjects across the various protocols employed by our group across various institutions.

6.3 WHAT ARE THE DIRECT OR INDIRECT ANTICIPATED BENEFITS TO STUDY PARTICIPANTS AND/OR SOCIETY?

Participants might benefit from education about research participation. The project invoves minimal risk to confidentiality or other personal rights or to physical or emotional health. Thus, the expected benefits outweigh the very minimal risks to participants.

Section 7: Full Board Assessment

7.1 DOES THE RESEARCH INVOLVE MICROWAVES/X-RAYS, OR GENERAL ANESTHESIA OR SEDATION?

☒ ***No***
☐ ***Yes***

7.2 DO RESEARCH ACTIVITIES INVOLVE PRISONERS, PREGNANT WOMEN, FETUSES, HUMAN IN VITRO FERTILIZATION, OR MENTALLY DISABLED PERSONS?

☒ ***No,*** go to question 7.3
☐ ***Yes,*** answer questions within table →

IF YES
This research involves: ☐ Prisoners ☐ Pregnant women ☐ Fetuses ☐ Human in vitro fertilization ☐ Mentally disabled persons

7.3 DOES THIS STUDY INVOLVE MORE THAN MINIMAL RISK TO STUDY PARTICIPANTS?

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily activities or during the performance of routine physical or psychological examinations or tests. Examples of research involving greater than minimal risk include collecting data about abuse or illegal activities. Note: if the project qualifies for Exempt review (http://www.irb.vt.edu/pages/categories.htm), it will not need to go to the Full Board.

☒ ***No***
☐ ***Yes***

IF YOU ANSWERED "YES" TO ***ANY ONE*** OF THE ABOVE QUESTIONS, 7.1, 7.2, OR 7.3, THE BOARD MAY REVIEW THE PROJECT'S APPLICATION MATERIALS AT ITS MONTHLY MEETING. VIEW THE FOLLOWING LINK FOR DEADLINES AND ADDITIONAL INFORMATION: http://www.irb.vt.edu/pages/deadlines.htm

Section 8: Confidentiality / Anonymity

For more information about confidentiality and anonymity visit the following link: http://www.irb.vt.edu/pages/confidentiality.htm

8.1 WILL PERSONALLY IDENTIFYING STUDY RESULTS OR DATA BE RELEASED TO ANYONE OUTSIDE OF THE RESEARCH TEAM?

For example – to the funding agency or outside data analyst, or participants identified in publications with individual consent

☐ ***No***
☒ ***Yes,*** to whom will identifying data be released? **Participant's identifying information (e.g., name, address, phone number) may be released to the FBRI at VTC administrative offices and the VT Controller's office in order to process the petty cash reimbursements for participant payments.**

8.2 WILL ANY STUDY FILES CONTAIN PARTICIPANT IDENTIFYING INFORMATION (E.G., NAME, CONTACT INFORMATION, VIDEO/AUDIO RECORDINGS)?

Note: if collecting signatures on a consent form, select "Yes."

☐ ***No,*** go to question 8.3
☒ ***Yes,*** answer questions within table

IF YES
Describe if/how the study will utilize study codes: **Using only ID numbers and initials and keeping all data in locked offices will protect confidentiality. Computer databases will have coded identifiers and all computers will be password protected.**
If applicable, where will the key [i.e., linked code and identifying information document (for instance, John Doe = study ID 001)] ***be stored and who will have access?*** **Master files linking subject names to study ID numbers will be accessible only to trained study team members delegated this access by the PI.** *Note: the key should be stored separately from subjects' completed data documents and accessibility should be limited.*
The IRB strongly suggests and may require that all data documents (e.g., questionnaire responses, interview

responses, etc.) do not include or request identifying information (e.g., name, contact information, etc.) from participants. If you need to link subjects' identifying information to subjects' data documents, use a study ID/code on all data documents.

8.3 WHERE WILL DATA BE STORED?

Examples of data - questionnaire, interview responses, downloaded online survey data, observation recordings, biological samples

All data and participant binders will be stored in a safe place to protect confidential participant information. Safe places will include locked filing cabinets or locked rooms accessible only to study personnel. The full names of participants will not be listed on the outside of binders to protect confidentiality of study participants.

Electronic data will be saved in secure, limited access shared drives on password-protected computers accessible only to the research team.

8.4 WHO WILL HAVE ACCESS TO STUDY DATA?

Access to study data will be limited to study personnel who have completed the Virginia Tech IRB Human Subjects Tutorial and who have been delegated the responsibilties of data collection, management, or analyses by the PI.

8.5 DESCRIBE THE PLANS FOR RETAINING OR DESTROYING THE STUDY DATA

Data collected from this study will be retained and destroyed in accordance with the center's policy that requires a 3-year retention period following final publication of the data.

8.6 DOES THIS STUDY REQUEST INFORMATION FROM PARTICIPANTS REGARDING ILLEGAL BEHAVIOR?

☐ ***No,*** go to question 9.1
☒ ***Yes,*** answer questions within table →

IF YES

Does the study plan to obtain a Certificate of Confidentiality?

☒ No
☐ Yes (Note: participants must be fully informed of the conditions of the Certificate of Confidentiality within the consent process and form)

For more information about Certificates of Confidentiality, visit the following link:
http://www.irb.vt.edu/pages/coc.htm

Section 9: Compensation

For more information about compensating subjects, visit the following link: http://www.irb.vt.edu/pages/compensation.htm

9.1 WILL SUBJECTS BE COMPENSATED FOR THEIR PARTICIPATION?

☐ ***No,*** go to question 10.1
☒ ***Yes,*** answer questions within table →

IF YES
What is the amount of compensation? **Compensation for participation will be as follows:** **$20.00 for completion of informed consent** **$40.00 for the assessment session** **$40.00 for each of the completed cigarette purchase session (7 total)** **$20.00 for the cigarette comparison session** **$75.00 bonus for completing all sessions** **$10 for cigarette purchase sessions that are discontinued due to situations outside of the of control of participants (i.e. a participant is eligble to begin a cigarette purchase session, but the session is discontinued due to an inability to successfully draw blood)** **Combined, the subjects could be compensated approximately $435 by completing all aspects of the experiment.** **To allow for payments that are both convenient and rapidly available, we may pay participants with reloadable prepaid cards through Greenphire ClinCard (www.greenphire.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At the beginning of the study, the participant will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to the account for that participant. Funds are immediately available when added and participants can check their balance as desired. This system will allow frequent, immediately available payments. Payments may also be made via check, however remote debit card payments will be used most often.**
Will compensation be prorated? ☒ Yes, please describe: **Subjects will be compensated based on what study procedures he/she has completed.** ☐ No, explain why and clarify whether subjects will receive full compensation if they withdraw from the study? *Unless justified by the researcher, compensation should be prorated based on duration of study participation. Payment must <u>not</u> be contingent upon completion of study procedures. In other words, even if the subject decides to withdraw from the study, he/she should be compensated, at least partially, based on what study procedures he/she has completed.*

Section 10: Audio / Video Recording

For more information about audio/video recording participants, visit the following link: http://www.irb.vt.edu/pages/recordings.htm

10.1 WILL YOUR STUDY INVOLVE VIDEO AND/OR AUDIO RECORDING?

☒ ***No,*** go to question 11.1
☐ ***Yes,*** answer questions within table →

IF YES
This project involves: ☐ Audio recordings only ☐ Video recordings only ☐ Both video and audio recordings
Provide compelling justification for the use of audio/video recording:

How will data within the recordings be retrieved / transcribed?
How and where will recordings (e.g., tapes, digital data, data backups) be stored to ensure security?
Who will have access to the recordings?
Who will transcribe the recordings?
When will the recordings be erased / destroyed?

Section 11: Research Involving Students

11.1 DOES THIS PROJECT INCLUDE STUDENTS AS PARTICIPANTS?

☒ ***No,*** go to question 12.1
☐ ***Yes,*** answer questions within table →

IF YES
Does this study involve conducting research with students of the researcher? ☐ No ☐ Yes, describe safeguards the study will implement to protect against coercion or undue influence for participation: *Note: if it is feasible to use students from a class of students not under the instruction of the researcher, the IRB recommends and may require doing so.*
Will the study need to access student records (e.g., SAT, GPA, or GRE scores)? ☐ No ☐ Yes

11.2 DOES THIS PROJECT INCLUDE <u>ELEMENTARY</u>, <u>JUNIOR</u>, OR <u>HIGH SCHOOL</u> STUDENTS?

☒ ***No,*** go to question 11.3
☐ ***Yes,*** answer questions within table →

IF YES
Will study procedures be completed during school hours? ☐ No ☐ Yes ***If yes,*** ***Students not included in the study may view other students' involvement with the research during school time as unfair. Address this issue and how the study will reduce this outcome:*** ***Missing out on regular class time or seeing other students participate may influence a student's decision to participate. Address how the study will reduce this outcome:***
Is the school's approval letter(s) attached to this submission? ☐ Yes ☐ No, project involves Montgomery County Public Schools (MCPS)

☐ No, explain why:

You will need to obtain school approval (if involving MCPS, click here: http://www.irb.vt.edu/pages/mcps.htm). Approval is typically granted by the superintendent, principal, and classroom teacher (in that order). Approval by an individual teacher is insufficient. School approval, in the form of a letter or a memorandum should accompany the approval request to the IRB.

11.3 DOES THIS PROJECT INCLUDE COLLEGE STUDENTS?

☒ ***No,*** go to question 12.1
☐ ***Yes,*** answer questions within table →

IF YES
Some college students might be minors. Indicate whether these minors will be included in the research or actively excluded: ☐ Included ☐ Actively excluded, describe how the study will ensure that minors will not be included:
Will extra credit be offered to subjects? ☐ No ☐ Yes ***If yes,*** ***What will be offered to subjects as an equal alternative to receiving extra credit without participating in this study?*** ***Include a description of the extra credit (e.g., amount) to be provided within question 9.1 ("IF YES" table)***

Section 12: Research Involving Minors

12.1 DOES THIS PROJECT INVOLVE MINORS (UNDER THE AGE OF 18 IN VIRGINIA)?

Note: age constituting a minor may differ in other States.

☒ ***No,*** go to question 13.1
☐ ***Yes,*** answer questions within table →

IF YES
Does the project reasonably pose a risk of reports of current threats of abuse and/or suicide? ☐ No ☐ Yes, thoroughly explain how the study will react to such reports: *Note: subjects and parents must be fully informed of the fact that researchers must report threats of suicide or suspected/reported abuse to the appropriate authorities within the Confidentiality section of the Consent, Assent, and/or Permission documents.*
Are you requesting a waiver of parental permission (i.e., parent uninformed of child's involvement)? ☐ No, ***both*** parents/guardians will provide their permission, if possible. ☐ No, ***only one*** parent/guardian will provide permission. ☐ Yes, describe below how your research meets ***all*** of the following criteria (A-D):

Criteria A - The research involves no more than minimal risk to the subjects:
Criteria B - The waiver will not adversely affect the rights and welfare of the subjects:
Criteria C - The research could not practicably be carried out without the waiver:
Criteria D - (Optional) Parents will be provided with additional pertinent information after participation:

Is it possible that minor research participants will reach the legal age of consent (18 in Virginia) while enrolled in this study?

☐ No
☐ Yes, will the investigators seek and obtain the legally effective informed consent (in place of the minors' previously provided assent and parents' permission) for the now-adult subjects for any ongoing interactions with the subjects, or analysis of subjects' data? If yes, explain how:

For more information about minors reaching legal age during enrollment, visit the following link:
http://www.irb.vt.edu/pages/assent.htm

*The procedure for obtaining assent from minors and permission from the minor's guardian(s) must be described in **Section 4** (Consent Process) of this form.*

Section 13: Research Involving Deception

For more information about involving deception in research and for assistance with developing your debriefing form, visit our website at http://www.irb.vt.edu/pages/deception.htm

13.1 DOES THIS PROJECT INVOLVE DECEPTION?

☒ ***No,*** go to question 14.1
☐ ***Yes,*** answer questions within table →

IF YES
Describe the deception:
Why is the use of deception necessary for this project?
Describe the debriefing process:
Provide an explanation of how the study meets <u>all</u> the following criteria (A-D) for an alteration of consent: Criteria A - The research involves no more than minimal risk to the subjects: Criteria B - The alteration will not adversely affect the rights and welfare of the subjects: Criteria C - The research could not practicably be carried out without the alteration: Criteria D - (Optional) Subjects will be provided with additional pertinent information after participation (i.e., debriefing for studies involving deception): *By nature, studies involving deception cannot provide subjects with a complete description of the study during the consent process; therefore, the IRB must allow (by granting an alteration of consent) a consent process which does not include, or which alters, some or all of the elements of informed consent.*
The IRB requests that the researcher use the title "Information Sheet" instead of "Consent Form" on the document used to obtain subjects' signatures to participate in the research. This will adequately reflect the fact that the subject cannot fully consent to the research without the researcher fully disclosing the true intent of the research.

Section 14: Research Involving Existing Data

14.1 WILL THIS PROJECT INVOLVE THE COLLECTION OR STUDY/ANALYSIS OF EXISTING DATA DOCUMENTS, RECORDS, PATHOLOGICAL SPECIMENS, OR DIAGNOSTIC SPECIMENS?

Please note: it is not considered existing data if a researcher transfers to Virginia Tech from another institution and will be conducting data analysis of an on-going study.

☒ ***No,*** you are finished with the application
☐ ***Yes,*** answer questions within table →

IF YES
From where does the existing data originate?
Provide a detailed description of the existing data that will be collected or studied/analyzed:
Is the source of the data public? ☐ No, continue with the next question ☐ Yes, you are finished with this application
Will any individual associated with this project (internal or external) have access to or be provided with existing data containing information which would enable the identification of subjects: ▪ ***Directly*** (e.g., by name, phone number, address, email address, social security number, student ID number), or ▪ ***Indirectly through study codes*** even if the researcher or research team does not have access to the master list linking study codes to identifiable information such as name, student ID number, etc or ▪ ***Indirectly through the use of information that could reasonably be used in combination to identify an individual*** (e.g., demographics) ☐ No, collected/analyzed data will be completely de-identified ☐ Yes, ***If yes,*** *Research will not qualify for exempt review; therefore, if feasible, written consent must be obtained from individuals whose data will be collected / analyzed, unless this requirement is waived by the IRB.* ***Will written/signed or verbal consent be obtained from participants prior to the analysis of collected data?*** -select one-

Proposed modifications must be approved by the IRB prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects.

Do not begin human subjects activities until you receive an IRB approval letter via email.

It is the Principal Investigator's responsibility to ensure all members of the research team who interact with research subjects, or collect or handle human subjects data have completed human subjects protection training prior to interacting with subjects, or handling or collecting the data.

----------END----------

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
v.8
August 28, 2019

Informed Consent for Participants
In Research Projects Involving Human Subjects

Title: Abuse liability of reduced nicotine content cigarettes: Experiment 1
Protocol: 16-472
Principal Investigators: Warren Bickel, Ph.D.
Institution: Fralin Biomedical Research Institute at VTC (formerly Virginia Tech Carilion Research Institute)

Purpose of the Study

You have been asked to come to this Virginia Tech facility because you may qualify for this research study. Your participation in this research study will help us learn more about the features of cigarettes that influence economic purchasing decisions.

Organization and Funding Source

This study is being conducted by the Fralin Biomedical Research Institute at VTC (formerly Virginia Tech Carilion Research Institute) and is funded by the National Institute on Drug Abuse/National Institutes of Health.

Number of Participants

We will enroll up to 250 participants in this study.

Participation

To participate in this study, you must be at least 18 years of age and a cigarette smoker. People under 110 lbs and women who are planning pregnancy, pregnant, lactating, or are not willing to use contraception during their enrollment are not eligible for this study. A urine screen will be collected from all females to test for pregnancy at the beginning of the study and every 6 weeks until the end of your participation.

To determine if it is appropriate for you to join this study, we will ask you to complete several questionnaires. We may stop your participation if there is evidence that you have a current unstable medical illness and/or an unmanaged psychiatric or neurological disorder. We will stop your participation if your answers or performance suggest that it is not appropriate for you to continue in the study. Violation of research center policies may result in the research team withdrawing you from the study. We may also stop your participation if you do not or are unable to complete any of the study procedures. We may also stop an ongoing session, or end your participation in the study because we have collected all the information we need. If you are a female, we may also stop your participation if at any point in the study you are identified as pregnant any time during the study. If you are withdrawn due to pregnancy during the course of the study, we will follow-up with you via phone to determine the outcome of the pregnancy (for example: were there complications, birth weight, and premature delivery).

Although you must be a current cigarette smoker to participate, participation in this study may increase your risk of harm relative to your current tobacco use.

You are free to stop your participation at any time. You may talk with other people about your decision to participate in this study, although we suggest avoiding confirming participation in this study to maintain confidentiality. You do not have to answer any questions that make you feel uncomfortable. There are no "right" or "wrong" answers; we want you to answer the questions honestly and thoughtfully. If it is appropriate for you to continue in the study, you will then complete questionnaires and computerized tasks that will measure some of your preferences and abilities.

Description and Procedures

This study will require you to complete approximately 10 visits to this Virginia Tech facility, including today's consent session.

One *(today's) consent session (approximately 1 hour)*. We will ask you some questions to make sure participation in the study is appropriate for you. We will also collect information (e.g. age, education) from you that we need to analyze our data. We will give you a detailed description of what it will be like to be in the study and answer any questions you have. We will also obtain a breath carbon monoxide (CO) reading and urine sample to test for pregnancy (females only). We will weigh you to ensure you weigh at least 110 lbs. We will measure your intentions of quitting smoking and/or obtaining treatment.

One *assessment session (approximately 1 hour)*. The first lab session will be an assessment session to collect information on substance use patterns and behavioral and cognitive tasks that we think may inform or compliment the results from the main study. This session may be scheduled the same day as the consent session or on a different day. These assessments will include:

- Breath and self-report measures of your recent nicotine product use
- Questionnaire about cigarette craving
- A measure of attention
- A questionnaire assessing how many nicotine products you'd purchase at different prices
- A measure of withdrawal symptoms
- A measure of your working memory
- A choice task asking you to choose between money or other commodities available at different delays

Seven *cigarette purchase sessions (approximately 1.5 hours each)*. During the seven cigarette purchase sessions (may be more if a session needs to be discontinued due to factors outside of your control, for example, the registered nurse or trained phlebotomist is unable to successfully draw blood) you will be asked to smoke 10 puffs of a cigarette in a ventilated room designed for this purpose. During each of these seven cigarette purchase sessions, you will consume cigarettes with a range of nicotine concentrations, with the maximum concentration approximately the same as commercially available cigarettes. Your preferred brand of conventional cigarettes will be used for one session and a nonusual brand, commercially-available cigarette will be used for one session; for other sessions investigational cigarettes (cigarettes that are made from genetically modified tobacco) will be used. The nicotine concentration of a cigarette for any

particular session will not be revealed to you until after the study. **You will be asked to abstain from consuming nicotine (for example, cigarettes, nicotine gum/lozenges, snus/dip, etc.) for 12 hours prior to each cigarette purchase session.** Abstinence will be verified with breath CO assessed at the beginning of the session. If you do not meet this criterion, you will be allowed to reschedule the session and try again, but after repeated failed attempts, your participation may be terminated. Two cigarette purchase sessions at least two days apart may be completed per week.

Each purchase session will begin with baseline ratings of breath CO, nicotine craving, current drug effect, and nicotine withdrawal symptoms. We will also collect blood samples (3 mL each) throughout the session so that we can test your plasma nicotine and cotinine levels (cotinine is a metabolite of nicotine). Blood will be drawn throughout the session by a registered nurse or trained phlebotomist. In addition to the baseline time point, the ratings of nicotine effect, breath CO, and 3 mL blood draws will also be collected immediately after the 5-minute administration period at minute 10, and again at minute 15, minute 20, minute 30, minute 45, and minute 60 (7 blood draws total per session). At minute 20 (10 min after the end of the consumption period), you will also complete hypothetical purchase tasks for the product you just consumed and some brief decision-making tasks, similar to the ones completed during the assessment session. You will be asked how many cigarette puffs of the cigarette you sampled that session you would purchase if they were available at different prices.

Blood samples will be de-identified (i.e., only labeled with an arbitrary ID) and brought to or sent for testing to a laboratory that offers such services (e.g., LabCorp or Solstas). Blood samples will only be tested for nicotine and the primary metabolite of nicotine (cotinine), after which they will be destroyed. In the event a researcher or other staff person is improperly exposed to your blood, your blood will be tested for the presence of HIV, the Hepatitis B Virus, and the Hepatitis C Virus. There will not be any cost to you for this test. The research team will follow proper procedures for testing and reporting as outlined by Virginia State Law, which includes sending the sample to a certified laboratory. Please note that, should your blood require testing, you will be informed of your test results and provided with the opportunity to receive appropriate and timely counseling. In addition, your results will be sent to the local health department.

One *cigarette comparison session (approximately 1.5 hours).* No blood will be drawn during this session. During this session, you will be provided an array of cigarettes you have used previously during this study. You will take one to two puffs of each cigarette and complete tasks similar to those completed during the cigarette purchase sessions. After puffing on all cigarettes, you will complete a series of tasks comparing the different cigarettes.

Risks/Discomforts/Inconveniences

One risk of participating in this study is possible embarrassment. This may result from answering questions that you consider sensitive. Some of our questions will ask for information about medical and psychiatric conditions and drug use. You may also experience discomfort from the blood draw sessions. In addition, loss of confidentiality is another potential risk of participation. We will make every effort to protect your confidentiality should you participate in this study. Any expenses accrued for seeking or receiving medical or mental health treatment will be the responsibility of the subject and not that of the research project, research team, or Virginia Tech.

Due to the investigative nature of this study, there may be other risks that are currently unknown.

If problems occur during the course of the study we will determine whether you should continue. If necessary, referrals will be provided. If you have questions concerning the study, please contact Warren K. Bickel, Ph.D., one of the Principal Investigators, at 540-526-2088 (office).

Possible Benefits
You may benefit from education about research participation. The project involves minimal risk to confidentiality or other personal rights or to physical or emotional health.

Voluntary Participation and Confidentiality
Your participation in this study is voluntary. You are free to decline participation in this study or withdraw from it at any time. If you are a Virginia Tech student, you may withdraw from the study without affecting your academic standing (i.e., your student status and evaluations will not be affected). We will act in accordance with the guidelines for the protection of human research participants issued by the Institutional Review Board (IRB) and Office of Research Compliance (ORC). Your identity on records relevant to this study will not be made public. Any publications resulting from this research will not mention your name or any other personally identifying information.

It is possible that the Institutional Review Board (IRB) may view this study's collected data for auditing purposes. The IRB is responsible for the oversight of the protection of human subjects involved in research. The sponsor (FBRI at VTC) or their appointed designees as well as the IRB, ORC, or other institutional oversight offices will be granted direct access to your original research records for verification of data. If your record is used or distributed for government purposes, this will be done under conditions that will protect your privacy. You will be informed of any significant new findings that may relate to your continued participation in this study.

The study team must release certain information to the appropriate authorities if at any time during the study there is concern that child abuse or elder abuse has possibly occurred or you disclose a desire to harm yourself or others.

Compensation
You will be compensated with a reloadable prepaid card issued by Greenphire ClinCard (www.myclincard.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At intake, you will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to your account. Funds are available within seconds when added and you can check your balance as desired. For your participation, you will be compensated:

- $20 for the consent session
- $40 for the assessment session
- $40 for each cigarette purchase session (7 total)
- $20 for the cigarette comparison session
- $75 completion bonus for completing all sessions

- $10 for any cigarette purchase session discontinued due to factors outside of your control

In total, you may earn up to approximately $435. Reimbursement may also be available to offset your expenses in traveling to this Virginia Tech facility.

If you receive compensation greater than $600.00 for research participation (not limited to this study), the amount received will be reported to the IRS and you will receive an IRS 1099 Form. We will collect social security numbers and retain them for IRS and auditing purposes.

Alternative to Participation

You do not have to participate in this study if you do not wish to. The alternative to participating in this study is not participating. Your employment status, student status, grades, extra-curricular activities, or medical treatment will not be affected in any way. This is not a treatment study. If you should choose to seek treatment either before or after your participation in this study, there are a number of options. Most types of treatment for nicotine dependence involve some form of counseling and medication. A national help line, 1-800-QUITNOW (1-800-784-8669) offers free assistance and referrals.

Questions or Concerns

If you have questions about this study, please contact the Principal Investigator, Dr. Warren Bickel at 540-526-2088 (telephone) or wkbickel@vtc.vt.edu (e-mail).

If you have any questions about your rights as a research subject or concerning a research related injury, you can call the Virginia Tech Institutional Review Board for the Protection of Human Subjects at 540-231-3732 (telephone) or irb@vt.edu (e-mail).

Subject's Responsibilities

I voluntarily agree to participate in this study. I have the following responsibilities:

- I will answer questions about health, and past and current substance and alcohol use
- I will abstain from using nicotine products for 12 hours prior to cigarette purchasing sessions
- I will complete laboratory assessments
- I will notify the researchers if I experience any discomfort or would like to discontinue participation from this study
- I will let the researchers know if I have any comments, questions or concerns regarding participation in this study

Subject's Permission/Statement of Consent

The purpose and voluntary nature of this study, as well as the potential benefits and risks that are involved have been explained to me. I have read the Consent Form and conditions of the project. I have been able to ask questions and express concerns, which have been satisfactorily responded to by the study team. I have been told that I will be given a copy of this consent form. I hereby acknowledge the above and give my informed and free consent to be a participant in this study. I recognize that I am not waiving any of my rights as a research participant by signing this consent form.

Participant's printed name	Signature	Date
Principal Investigator's/Designee's printed name	Signature	Date
Person obtaining informed consent	Signature	Date

VirginiaTech

Institutional Review Board
Research Protocol

Once complete, upload this form as a Word document to the IRB Protocol Management System: https://secure.research.vt.edu/irb

Section 1: General Information

1.1 DO ANY OF THE INVESTIGATORS OF THIS PROJECT HAVE A REPORTABLE CONFLICT OF INTEREST? (http://www.irb.vt.edu/pages/researchers.htm#conflict)

☒ ***No***
☐ ***Yes,*** explain:

1.2 WILL THIS RESEARCH INVOLVE COLLABORATION WITH ANOTHER INSTITUTION?

☐ ***No,*** go to question 1.3
☒ ***Yes,*** answer questions within table →

IF YES
Provide the name of the institution [for institutions located overseas, please also provide name of country]***:*** **Carilion Hospital**
Indicate the status of this research project with the other institution's IRB: ☐ Pending approval ☐ Approved ☐ Other institution does not have a human subject protections review board ☒ Other, explain: **Human subject activities covered in this protocol.**
Will the collaborating institution(s) be engaged in the research? (http://www.hhs.gov/ohrp/policy/engage08.html) ☒ No ☐ Yes
Will Virginia Tech's IRB review all human subject research activities involved with this project? ☐ No, provide the name of the primary institution: ☒ Yes *Note: primary institution = primary recipient of the grant or main coordinating center*

1.3 IS THIS RESEARCH FUNDED?

☐ ***No,*** go to question 1.4
☒ ***Yes,*** answer questions within table →

IF YES
Provide the name of the sponsor [if NIH, specify department]: **NIH/National Institute on Drug Abuse**
Is this project receiving federal funds? ☐ No ☒ Yes ***If yes,***

Does the grant application, OSP proposal, or "statement of work" related to this project include activities involving human subjects that are <u>not</u> covered within this IRB application?

☐ No, all human subject activities are covered in this IRB application
☐ Yes, however these activities will be covered in future VT IRB applications, these activities include:
☒ Yes, however these activities have been covered in past VT IRB applications, the IRB number(s) are as follows: **16-472**
☐ Yes, however these activities have been or will be reviewed by another institution's IRB, the name of this institution is as follows:
☐ Other, explain:

***Is* Virginia Tech the primary awardee or the coordinating center of this grant?**

☐ No, provide the name of the primary institution:
☒ Yes

1.4 DOES THIS STUDY INVOLVE CONFIDENTIAL OR PROPRIETARY INFORMATION (OTHER THAN HUMAN SUBJECT CONFIDENTIAL INFORMATION), OR INFORMATION RESTRICTED FOR NATIONAL SECURITY OR OTHER REASONS BY A U.S. GOVERNMENT AGENCY?

For example – government / industry proprietary or confidential trade secret information

☐ ***No***
☒ ***Yes,*** describe: **This project uses investigational reduced nicotine cigarettes manufactured by the National Institute on Drug Abuse for use in resarch studies. NIDA holds the proprietary master file for these cigarettes, and their use in research studies needs to be approved by the FDA Center for Tobacco Products. Under this oversight, any serious adverse events that occur with these products will be reported to the FDA.**

1.5 DOES THIS STUDY INVOLVE SHIPPING ANY TANGIBLE ITEM, BIOLOGICAL OR SELECT AGENT OUTSIDE THE U.S?

☒ ***No***
☐ ***Yes***

Section 2: Justification

2.1 DESCRIBE THE BACKGROUND, PURPOSE, AND ANTICIPATED FINDINGS OF THIS STUDY:

Abuse liability of reduced nicotine content cigarettes: Experiment 2
IRB
v.10
04/08/19

With the recently acquired mandate of the FDA to regulate the rapidly increasing market of tobacco products, research that can inform these regulations is vital. Before modifying the tobacco product marketplace through regulatory action, it is important to understand how specific features of tobacco products influence the choices to purchase and consume that product. The long-term goal of this line of research is to build an evaluative framework to assess how different aspects of tobacco products that may be subject to regulatory action (e.g., flavor, nicotine content, packaging) influence decisions to purchase and consume those products across a range of prices. To craft effective regulations, it is important to understand how specific features of tobacco products that may be subject to regulatory action influence the choice to purchase and consume that product.

Economic demand analyses quantify the relationship between the cost of a commodity and population-level measures of consumption of that commodity. Behavioral economic demand analyses are analogous to these population-level analyses, but can be used to understand the level of motivation to consume a product on either an individual or small group level, including cigarettes (Bickel et al., 1995; MacKillop et al.,

2008). This level of analysis allows for experimental manipulations to be made on variables of interest. By quantifying how consumption decreases as costs to obtain and consume a product increase, important indices of demand are obtained. These indices can be grouped into two main measures of consumption, demand intensity and demand elasticity, which are associated with use level and dependence severity (MacKillop et al., 2008, 2009, 2010; Murphy et al., 2011). Demand intensity is the amount of the commodity consumed when available at a very low cost approaching free, and demand elasticity quantifies the degree to which the individual is willing to increase monetary or effort-based expenditures to maintain the same level of consumption as costs increase. Elasticity of demand has been shown to be a characteristic of the drug itself and independent of drug dose for many drugs including nicotine (Bickel et al., 1991; Hursh & Roma, 2013; Hursh & Silberberg, 2008; Hursh & Winger, 1995).

A fundamental observation of economics is that the type and number of products in a marketplace can alter a commodity's demand elasticity as well as the type and degree of interaction among those products. As a result, the ability to achieve the tobacco control goals of reducing the consumption of a particular product may be enhanced or diminished via the economic processes of substitution and complementarity (see Bickel, DeGrandpre, et al., 1995 for a review). Substitution, complementarity, and independence are measured by cross-price elasticity of demand and are represented by elasticity slopes that are positive, negative, or near zero, respectively. Studies to date have almost exclusively examined only pairs of products and in very few cases three concurrent commodities. Relevant to this application, the investigators examined the interaction of three commodities in one of their prior studies (Johnson, et al., 2004). Specifically, smokers had access to conventional cigarettes, reduced-nicotine cigarettes, and nicotine gum. When the price of conventional cigarettes increased, consumption of both reduced-nicotine cigarettes and nicotine gum increased even though their prices were fixed. Thus, reduced-nicotine cigarettes and nicotine gum functioned as substitutes for conventional cigarettes. Indeed, by concurrently using both products, the smoker could reproduce different aspects of the conventional cigarette experience by consuming the reduced-nicotine cigarette (i.e., sensory effects associated with combustible tobacco smoke inhalation) and nicotine gum (i.e., central effects associated with nicotine ingestion). Importantly, reduced-nicotine cigarettes functioned as a better substitute than gum when each was offered as a substitute alone (the use of denicotinized cigarettes increased the most).

To inform how various products may interact, we have developed and tested a novel method called the Experimental Tobacco Marketplace. The Experimental Tobacco Marketplace is a systematic extension of similar marketplace methods used with other consumer products (e.g., food marketplaces used in obesity and other nutrition-related research; Epstein, Dearing, Roba, & Finkelstein, 2010). In experimental marketplaces, multiple products are available and the experimenter controls the prices for each. These marketplaces can be either physical or virtual stores (similar to online retailers) and permit the examination of demand elasticity and intensity and degree of substitution or complementarity in consumer behavior under conditions that approximate naturalistic settings.

This study will extend findings from an ongoing project examining the effects of different concentrations of nicotine in cigarettes (0.4mg/g, 1.4mg/g, 2.5mg/g, 5.6mg/g, 17.4mg/g) and blood nictotine absorption on laboratory behavioral economic demand measures. Employing this innovative Experimental Tobacco Marketplace, we propose to examine reduced-nicotine cigarettes under the following conditions: 1) control conditions where lower dose nicotine cigarettes are the only available product in the Experimental Tobacco Marketplace and where the tobacco marketplace is similar to the current real-world marketplace (i.e., no lower dose nicotine cigarettes, but a variety of other tobacco products); 2) lower dose nicotine cigarettes are available with a number of other nicotine products excluding conventional cigarettes; and 3) lower dose nicotine cigarettes are available with a number of other nicotine products including conventional cigarettes.

2.2 EXPLAIN WHAT THE RESEARCH TEAM PLANS TO DO WITH THE STUDY RESULTS:

For example - publish or use for dissertation

The research team intends to publish the results of the current study in peer-reviewed journals.

Section 3: Recruitment

3.1 DESCRIBE THE SUBJECT POOL, INCLUDING INCLUSION AND EXCLUSION CRITERIA AND NUMBER OF SUBJECTS:

Examples of inclusion/exclusion criteria - gender, age, health status, ethnicity

Up to 350 current cigarette smokers will be recruited from the community in areas of Virginia. Eligible participants will be 18 to 65 years old, smoke from 5 to 40 cigarettes per day, have a breath carbon monoxide (CO) level of at least 10 ppm at intake, and have no immediate plans to quit smoking. Females who are able to become pregnant and are: planning pregnancy, pregnant, lactating, or not willing to use contraception for the purpose of preventing pregnancy during the study will be excluded from participation. Individuals who have plans to move out of the area during the course of the experiment will also be excluded. Use of other tobacco/nicotine products will not be exclusionary. These minimally restrictive inclusion/exclusion criteria will allow for a broad range of participants and increase the generalizability to tobacco regulation of our eventual results. Participants who are not eligible may be rescreened for eligibility after at least 30 days has passed.

3.2 WILL EXISTING RECORDS BE USED TO IDENTIFY AND CONTACT / RECRUIT SUBJECTS?

Examples of existing records - directories, class roster, university records, educational records

☐ ***No,*** go to question 3.3
☒ ***Yes,*** answer questions within table →

IF YES
Are these records private or public? ☐ Public ☒ Private, describe the researcher's privilege to the records: **Participants will be contacted if they have given prior permission (through a previous informed consent form) or by completion of a confidential pre-screening questionnaire.**
Will student, faculty, and/or staff records or contact information be requested from the University? ☒ No ☐ Yes, visit the following link for further information: http://www.policies.vt.edu/index.php (policy no. 2010)

3.3 DESCRIBE RECRUITMENT METHODS, INCLUDING HOW THE STUDY WILL BE ADVERTISED OR INTRODUCED TO SUBJECTS:

Participants will be recruited from the community via advertisements such as posted flyers, internet (e.g., Facebook or other websites), etc. To the extent possible, we will attempt to minimize obstacles to participation. For example, travel barriers may be addressed by providing transportation or parking costs for participants, and scheduling barriers will be minimized by offering a flexible study visit schedule. Compensation may be provided for travel costs and time. All methods and measures will be conducted using standard operating procedures, and all staff (including recruitment staff) will be provided with online human subjects training. We have a history of successful recruitment of cigarette smokers into research programs. All participants will enroll on a voluntary basis.

3.4 PROVIDE AN EXPLANATION FOR CHOOSING THIS POPULATION:

Note: the IRB must ensure that the risks and benefits of participating in a study are distributed equitably among the general population and that a specific population is not targeted because of ease of recruitment.

Cigarette smokers will be recruited for this study. This population was chosen because the current experiment entails smoking cigarettes. Non-smokers would not be appropriate because nicotine and tobacco smoke may make individuals that do not regularly smoke feel ill. Women who can and may become pregnant (e.g., able to become pregnant and planning to become pregnant or don't use contraceptives) are excluded as the current tobacco products are investigational and risks to developing fetuses are unknown. Otherwise healthy individuals are sought to minimize any ill effects that exposure to nicotine and cigarette smoke may cause.

Section 4: Consent Process

For more information about consent process and consent forms visit the following link: http://www.irb.vt.edu/pages/consent.htm

If feasible, researchers are advised and may be required to obtain signed consent from each participant unless obtaining signatures leads to an increase of risk (e.g., the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting in a breach of confidentiality). Signed consent is typically not required for low risk questionnaires (consent is implied) unless audio/video recording or an in-person interview is involved. If researchers will not be obtaining signed consent, participants must, in most cases, be supplied with consent information in a different format (e.g., in recruitment document, at the beginning of survey instrument, read to participant over the phone, information sheet physically or verbally provided to participant).

4.1 CHECK ALL OF THE FOLLOWING THAT APPLY TO THIS STUDY'S CONSENT PROCESS:

- ☐ Verbal consent will be obtained from participants
- ☒ Written/signed consent will be obtained from participants
- ☐ Consent will be implied from the return of completed questionnaire. Note: The IRB recommends providing consent information in a recruitment document or at the beginning of the questionnaire (if the study only involves implied consent, skip to Section 5 below)
- ☐ Other, describe:

4.2 PROVIDE A GENERAL DESCRIPTION OF THE PROCESS THE RESEARCH TEAM WILL USE TO OBTAIN AND MAINTAIN INFORMED CONSENT:

Potential participants will be provided with the written consent form prior to visiting a Virginia Tech facility (e.g., by email), if they wish. They will also be given additional time in a quiet room in a Virginia Tech facility to read the form. Virginia Tech affiliated research staff will review each element of the written consent form with the potential participant. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. They will be encouraged to speak with whomever they wish before making this decision. Staff will reiterate that the potential participant can choose to decline participation in the study at that time or at any time thereafter without consequence. The potential participant and person obtaining consent will sign the consent form after the potential participant verbally states that s/he understands the conditions of the study, has no more questions, and chooses to participate.

4.3 WHO, FROM THE RESEARCH TEAM, WILL BE OVERSEEING THE PROCESS AND OBTAINING CONSENT FROM SUBJECTS?

Study team members that have been delegated this responsibility by the PI.

4.4 WHERE WILL THE CONSENT PROCESS TAKE PLACE?

In a quiet room in a Virginia Tech facility.

4.5 DURING WHAT POINT IN THE STUDY PROCESS WILL CONSENTING OCCUR?

Note: unless waived by the IRB, participants must be consented before completing any study procedure, including screening questionnaires.

Consenting will occur prior to any study procedures.

4.6 IF APPLICABLE, DESCRIBE HOW THE RESEARCHERS WILL GIVE SUBJECTS AMPLE TIME TO REVIEW THE CONSENT DOCUMENT BEFORE SIGNING:

Note: typically applicable for complex studies, studies involving more than one session, or studies involving more of a risk to subjects.

Prior to visiting the lab, participants will be given the option to reveive a copy of the consent form before

attending a consent session. They will be able to receive the consent copy via e-mail, mail, or in person if they wish. The potential participant will be given the opportunity to ask questions and will have as much time as they need to decide whether they would like to participate in the study. They will be encouraged to speak with whomever they wish before making this decision.

☐ Not applicable

Section 5: Procedures

5.1 PROVIDE A STEP-BY-STEP THOROUGH EXPLANATION OF ALL STUDY PROCEDURES EXPECTED FROM STUDY PARTICIPANTS, INCLUDING TIME COMMITMENT & LOCATION:

We will first ask potential participants a series of brief screening questions to determine whether they will likely meet eligibility criteria. Individuals who are eligible based on the screening questionnaire will be scheduled for an informed consent session. Note that this phone screening script is used in many studies conducted here and is a broad screening to examine eligibility in a number of ongoing studies. The phone screen script is approved in VT IRB Protocol: 13-294.

The current study will take place over approximately 6 laboratory sessions at a Virginia Tech facility including the consent session (approximately 1 hour). Following informed consent, participants may also be asked to leave a baseline CO sample and urine sample (females only). The urine sample will be tested for pregnancy in females. Weight will also be measured. We have included three screening questions that ask about intentions to quit and desire to seek treatment. If a participant reports discordant answers on the intentions to quit or seek treatment questions (e.g., indicates no plans to quit but expresses an interest in treatment), we will ask a clarifying question that more directly assesses our stated exclusionary criteria of an immediate plan to quit smoking. For these participants, a question will appear that asks: "You expressed some interest in either quitting smoking or smoking cessation treatment. Do you have plans for a quit attempt in the next 30 days?" If the participant answers that s/he plans to quit, s/he will be excluded from participation after information is gathered from the assessment session but before cigarettes are provided, and provided the 1-800-QUITNOW (1-800-784-8669) hotline, which can connect callers to a variety of local resources for quitting. However, the participant will be allowed to continue the experiment if there are no plans to quit in the next 30 days. All participants will complete the assessment session and only eligible participants who do not express immediate plans to quit will receive the sampling period cigarettes and return to complete the rest of the experiment. Thus, the total time commitment expected will be approximately 5 weeks.

Assessment session (approximately 1 hour). The first lab session will be the assessment session to collect information from participants on substance use patterns and severity, as well as the results of behavioral and cognitive tasks that we think may inform or compliment the results from the main study (see appendix for examples). This may be on the same day as the consent session. All participants will complete these computerized tasks, but only eligible participants (e.g., who do not express immediate plans to quit) will be provided a 5-day supply of the experimental cigarette at the end of this session. In addition, only eligible participants will complete a demonstration of the Experimental Tobacco Marketplace, so that participants will experience the types of questions that will be asked during these sessions (see below). The experimental cigarette will be one of the following concentrations, which will be determined by random assignment initially: 0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, and 17.4 mg/g. After initial random assignment, an algorithm taking into account various demographic measures (for example, number of conventional cigarettes smoked per day, gender, nicotine yield of usual brand cigarette) will be used to assign participants to groups with the purpose of achieving balanced groups (given the between-subject design). They will be asked to use the provided cigarettes instead of their usual brand for five days. This sampling period is important to increase the generalizability of results obtained during the Experimental Tobacco Marketplace sessions and especially to allow participants to make informed decisions regarding the experimental cigarette to which they will be assigned for the remainder of the study. Participants will be informed that some of the cigarettes they will be using during the course of the study may have reduced nicotine, but will not be told the explicit concentration. If the participant is eligible to continue on through the study, the conclusion of the assessment session will be occur when the participant returns the next session and reports how many experimental and non-experimental cigarettes they used during that past week. After this information is obtained, the participant will complete the first Experimental Tobacco Marketplace session.

Experimental Tobacco Marketplace sessions (4 sessions, approximately 30-60 minutes each). Each participant will be initially randomly assigned to one of the following concentration groups: 0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, and 17.4 mg/g. Random assignment will be double blind, such that the participant and any research staff directly interacting with the participant will not be aware of the assigned cigarette concentration (but as indicated previously, an algorithm will then be used to assign participants to strive for equally balanced groups on demographic and cigarette measures). However, as mentioned in the assessment sessions, participants will be informed that some of the cigarettes they will be using during the course of the study may have reduced-nicotine. In the purchasing scenario, labels will differentiate the experimental cigarettes from the conventional cigarettes. For reference, conventional cigarettes sold in stores range from ~16-19 nicotine mg/g (Malson et al., 2001). During these four sessions, participants will sit in front of a computer and respond to an online marketplace where they will be able to "purchase" a variety of nicotine products (e.g., conventional cigarettes, nicotine gum, snus, electronic cigarettes). Importantly, the marketplace interface mimics what participants might encounter if they shopped online for these products. In order to obtain the behavioral economic measures described earlier (e.g., demand intensity, substitutability, complementarity), in each session participants will complete a series of purchasing scenarios where the price of cigarettes (experimental and/or conventional) is manipulated (approximately 6 prices) and all other nicotine products remain at a constant price. Participants will be given an income equal to five days worth of their typical expenditure on cigarettes and will be asked to make purchases for the following five days. They will be able to keep the remaining balance from the income. At the end of each marketplace session, the participant will receive the nicotine products they purchased from one randomly selected pricing scenario. After at least approximately five days following each marketplace condition, participants will return to purchase more cigarettes and report the use of experimenter provided and non-experimenter provided tobacco/nicotine products, with the ability to return any unused experimenter provided products for a refund. At the end of the fourth laboratory marketplace session, participants will complete a brief questionnaire (Stages of Change Readiness and Treatment Eagerness Scale-S; Miller & Tonigan, 1996; Park et al., 2012).

The four marketplace sessions (presented in a counterbalanced order) will consist of the following conditions:
1. Price of conventional cigarettes will be manipulated with other nicotine products at a constant price
2. Price of experimental cigarettes will be manipulated with no other products available
3. Price of experimental cigarettes will be manipulated with other nicotine products at a constant price
4. A blend of 1 and 3 such that price of conventional cigarettes and experimental cigarettes will be simultaneously available (one will be manipulated while the other is held constant and vice versa) with other nicotine products at a constant price

At the last in-lab Experimental Tobacco Marketplace session participants may be recruited for an addendum to this study, which includes two additional sessions (described below). If the participant agrees and is a female, she may be retested for pregnancy at this time. Participants will only be approached and recruited contingent upon approval by the FDA Center for Tobacco Products for these additional sessions.

Post-marketplace Sampling (1 session; approximately 15-30 minutes): After at least approximately five days following the fourth marketplace session, participants may return to the laboratory for the ability to return any unused experimenter provided products for a refund and report the number of tobacco products used since the previous session. During this session, all participants, regardless of assigned investigational cigarette concentration, will be provided five-days' worth each of the "high" (17.4 mg/g) and "low" (0.4 mg/g) investigational cigarette. In addition to the "Investigational Tobacco Product" label, these cigarettes will be labeled with arbitrary codes e.g., "A" and "B" (randomized across participants as to which concentration the code reflects); for subsequent tasks, participants will be told that cigarette "C" refers to the investigational cigarette they were assigned to at the onset of the study. Participants will be told to use only these cigarettes for the following five days.

Post-sampling (1 session; approximately 30-60 minutes): After at least approximately five days following the post-marketplace sampling session, participants may return to the lab to report the number investigational cigarettes and other tobacco products used since the previous session. Participants will complete a series of tasks similar to those administered during the assessment session and experimental tobacco marketplace sessions, except specific to each of the investigational cigarette concentrations the participant has experienced during the course of the study. Specifically, participants will complete a discrete choice procedure (e.g., Would you rather have Cigarette A or Cigarette B), cigarette ranking (e.g., rank ordering the three cigarettes), a multiple choice procedure, at least one of the regulatory environment conditions from

the experimental tobacco marketplace sessions (except they will not actually receive the products they purchase; only hypothetical purchases), and simulated purchase tasks with the investigational cigarettes in isolation and in combination.

All participants will be provided the 1-800-QUITNOW (1-800-784-8669) hotline, which can connect callers to a variety of local resources for quitting, at the end of their participation.

5.2 DESCRIBE HOW DATA WILL BE COLLECTED AND RECORDED:

All data will be collected and recorded with custom-built computer programs and/or standardized paper forms by trained study staff.

5.3 DOES THE PROJECT INVOLVE ONLINE RESEARCH ACTIVITES (INCLUDES ENROLLMENT, RECRUITMENT, SURVEYS)?

View the "Policy for Online Research Data Collection Activities Involving Human Subjects" at http://www.irb.vt.edu/documents/onlinepolicy.pdf

☐ ***No,*** go to question 6.1
☒ ***Yes,*** answer questions within table →

IF YES

Identify the service / program that will be used:

☐ www.survey.vt.edu, go to question 6.1
☐ Blackboard, go to question 6.1
☐ Center for Survey Research, go to question 6.1
☒ Other

IF OTHER:

Name of service / program: **REDCap, Craigslist, Facebook**
URL: **http://www.redcap.com/ , https://www.craigslist.org/, https://www.facebook.com**
This service is…

☐ Included on the list found at: http://www.irb.vt.edu/pages/validated.htm
☐ Approved by VT IT Security
☒ An external service with proper SSL or similar encryption (https://) on the login (if applicable) and all other data collection pages.
☐ None of the above (note: only permissible if this is a collaborative project in which VT individuals are only responsible for data analysis, consulting, or recruitment)

Section 6: Risks and Benefits

6.1 WHAT ARE THE POTENTIAL RISKS (E.G., EMOTIONAL, PHYSICAL, SOCIAL, LEGAL, ECONOMIC, OR DIGNITY) TO STUDY PARTICIPANTS?

One risk of participation is embarrassment that may come from answering sensitive questions related to medical, psychiatric, and/or drug use history. Loss of confidentiality is another risk of participation. Finally, there may be the potential for increased withdrawal symptoms related to less than usual nicotine intake.

6.2 EXPLAIN THE STUDY'S EFFORTS TO REDUCE POTENTIAL RISKS TO SUBJECTS:

Participants will be screened, using medical history and structured interviews, for a history of medical contraindications (e.g., pregnancy), and current unstable medical illnesses. The study will occur in one of our Virginia Tech facilities. Participants will be free to withdraw from the study at any time, and their refusal to continue will not affect other medical care associated with Carilion. Participants will be told that a risk may include increased withdrawal symptoms related to less than usual nicotine intake. In addition, if participants develop medical problems or experience adverse events during the course of the study,

assessments to determine whether participants should continue in the study and/or continue to use study products will be conducted and necessary referrals will be provided. Using only ID numbers and keeping all data in secure locations and/or in locked offices accessible only to trained study team members will protect confidentiality. Computer databases will have coded identifiers. These screening, monitoring, and confidentiality procedures have been in effect for more than 10 years and for more than 2,000 subjects across the various protocols employed by our group across various institutions.

6.3 WHAT ARE THE DIRECT OR INDIRECT ANTICIPATED BENEFITS TO STUDY PARTICIPANTS AND/OR SOCIETY?

Participants might benefit from education about research participation. The project invoves minimal risk to confidentiality or other personal rights or to physical or emotional health. Thus, the expected benefits outweigh the very minimal risks to participants.

Section 7: Full Board Assessment

7.1 DOES THE RESEARCH INVOLVE MICROWAVES/X-RAYS, OR GENERAL ANESTHESIA OR SEDATION?

☒ ***No***
☐ ***Yes***

7.2 DO RESEARCH ACTIVITIES INVOLVE PRISONERS, PREGNANT WOMEN, FETUSES, HUMAN IN VITRO FERTILIZATION, OR MENTALLY DISABLED PERSONS?

☒ ***No,*** go to question 7.3
☐ ***Yes,*** answer questions within table →

IF YES
This research involves:
☐ Prisoners
☐ Pregnant women ☐ Fetuses ☐ Human in vitro fertilization
☐ Mentally disabled persons

7.3 DOES THIS STUDY INVOLVE MORE THAN MINIMAL RISK TO STUDY PARTICIPANTS?

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily activities or during the performance of routine physical or psychological examinations or tests. Examples of research involving greater than minimal risk include collecting data about abuse or illegal activities. Note: if the project qualifies for Exempt review (http://www.irb.vt.edu/pages/categories.htm), it will not need to go to the Full Board.

☒ ***No***
☐ ***Yes***

IF YOU ANSWERED "YES" TO ***ANY ONE*** OF THE ABOVE QUESTIONS, 7.1, 7.2, OR 7.3, THE BOARD MAY REVIEW THE PROJECT'S APPLICATION MATERIALS AT ITS MONTHLY MEETING. VIEW THE FOLLOWING LINK FOR DEADLINES AND ADDITIONAL INFORMATION: http://www.irb.vt.edu/pages/deadlines.htm

Section 8: Confidentiality / Anonymity

For more information about confidentiality and anonymity visit the following link: http://www.irb.vt.edu/pages/confidentiality.htm

8.1 WILL PERSONALLY IDENTIFYING STUDY RESULTS OR DATA BE RELEASED TO ANYONE OUTSIDE OF THE RESEARCH TEAM?

For example – to the funding agency or outside data analyst, or participants identified in publications with individual consent

☐ ***No***

☒ ***Yes,*** to whom will identifying data be released? **Participant's identifying information (e.g., name, address, phone number) may be released to the VTCRI administrative offices and the VT Controller's office in order to process the petty cash reimbursements for participant payments.**

8.2 WILL ANY STUDY FILES CONTAIN PARTICIPANT IDENTIFYING INFORMATION (E.G., NAME, CONTACT INFORMATION, VIDEO/AUDIO RECORDINGS)?

Note: if collecting signatures on a consent form, select "Yes."

☐ ***No,*** go to question 8.3

☒ ***Yes,*** answer questions within table →

IF YES
Describe if/how the study will utilize study codes: **Using only ID numbers and initials and keeping all data in locked offices will protect confidentiality. Computer databases will have coded identifiers and all computers will be password protected.**
If applicable, where will the key [i.e., linked code and identifying information document (for instance, John Doe = study ID 001)] ***be stored and who will have access?*** **Master files linking subject names to study ID numbers will be accessible only to trained study team members delegated this access by the PI.** *Note: the key should be stored separately from subjects' completed data documents and accessibility should be limited.*
The IRB strongly suggests and may require that all data documents (e.g., questionnaire responses, interview responses, etc.) do not include or request identifying information (e.g., name, contact information, etc.) from participants. If you need to link subjects' identifying information to subjects' data documents, use a study ID/code on all data documents.

8.3 WHERE WILL DATA BE STORED?

Examples of data - questionnaire, interview responses, downloaded online survey data, observation recordings, biological samples

All data and participant binders will be stored in a safe place to protect confidential participant information. Safe places will include locked filing cabinets or locked rooms accessible only to study personnel. The full names of participants will not be listed on the outside of binders to protect confidentiality of study participants.

Electronic data will be saved in secure, limited access shared drives on password-protected computers accessible only to the research team.

8.4 WHO WILL HAVE ACCESS TO STUDY DATA?

Access to study data will be limited to study personnel who have completed the Virginia Tech IRB Human Subjects Tutorial and who have been delegated the responsibilties of data collection, management, or analyses by the PI.

8.5 DESCRIBE THE PLANS FOR RETAINING OR DESTROYING THE STUDY DATA

Data collected from this study will be retained and destroyed in accordance with the center's policy that requires a 3-year retention period following final publication of the data.

8.6 DOES THIS STUDY REQUEST INFORMATION FROM PARTICIPANTS REGARDING ILLEGAL BEHAVIOR?

☐ ***No,*** go to question 9.1
☒ ***Yes,*** answer questions within table

IF YES
Does the study plan to obtain a Certificate of Confidentiality? ☒ No ☐ Yes (Note: participants must be fully informed of the conditions of the Certificate of Confidentiality within the consent process and form) *For more information about Certificates of Confidentiality, visit the following link:* *http://www.irb.vt.edu/pages/coc.htm*

Section 9: Compensation

For more information about compensating subjects, visit the following link: http://www.irb.vt.edu/pages/compensation.htm

9.1 WILL SUBJECTS BE COMPENSATED FOR THEIR PARTICIPATION?

☐ ***No,*** go to question 10.1
☒ ***Yes,*** answer questions within table

IF YES
What is the amount of compensation? **Compensation for participation will be as follows:** **$20.00 for completion of informed consent** **$40.00 for the assessment session (for those who are eligible to go on during the study, compensation will be provided in the following way: $10 for the initial assessment session and $30 for returning and reporting the products used during the sampling period)** **$20.00 compensation for time spent completing each of the Experimental Tobacco Marketplace sessions** **$75.00 bonus for completing all aspects of the experiment** **Participants may also receive the following compensation if they are recruited for and agree to participate in the addendum:** **$10 for the post-marketplace sampling session** **$20 for the post-sampling session** **Combined, the subjects could be compensated approximately up to $215 - $245 (if subjects complete the addendeum) by completing all aspects of the experiment.** **In addition, participants will receive between approximately $6.25 and $50.00 each purchase session to purchase tobacco/nicotine products. The amount each participant receives will be proportional to his/her real-world cigarette expenditure. These amounts will not be advertised as, or considered, compensation.** **To allow for payments that are both convenient and rapidly available, we may pay participants with reloadable prepaid cards through Greenphire ClinCard (www.greenphire.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At the beginning of the study, the participant will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to the account**

for that participant. Funds are immediately available when added and participants can check their balance as desired. This system will allow frequent, immediately available payments. Payments may also be made via check, however remote debit card payments will be used most often.
Will compensation be prorated? ☒ Yes, please describe: **Subjects will be compensated based on what study procedures he/she has completed.** ☐ No, explain why and clarify whether subjects will receive full compensation if they withdraw from the study? *Unless justified by the researcher, compensation should be prorated based on duration of study participation. Payment must <u>not</u> be contingent upon completion of study procedures. In other words, even if the subject decides to withdraw from the study, he/she should be compensated, at least partially, based on what study procedures he/she has completed.*

Section 10: Audio / Video Recording

For more information about audio/video recording participants, visit the following link: http://www.irb.vt.edu/pages/recordings.htm

10.1 WILL YOUR STUDY INVOLVE VIDEO AND/OR AUDIO RECORDING?

☒ ***No,*** go to question 11.1
☐ ***Yes,*** answer questions within table →

IF YES
This project involves: ☐ Audio recordings only ☐ Video recordings only ☐ Both video and audio recordings
Provide compelling justification for the use of audio/video recording:
How will data within the recordings be retrieved / transcribed?
How and where will recordings (e.g., tapes, digital data, data backups) be stored to ensure security?
Who will have access to the recordings?
Who will transcribe the recordings?
When will the recordings be erased / destroyed?

Section 11: Research Involving Students

11.1 DOES THIS PROJECT INCLUDE STUDENTS AS PARTICIPANTS?

☒ ***No,*** go to question 12.1
☐ ***Yes,*** answer questions within table →

IF YES
Does this study involve conducting research with students of the researcher? ☐ No ☐ Yes, describe safeguards the study will implement to protect against coercion or undue influence for participation: *Note: if it is feasible to use students from a class of students not under the instruction of the researcher, the IRB recommends and may require doing so.*
Will the study need to access student records (e.g., SAT, GPA, or GRE scores)? ☐ No ☐ Yes

11.2 DOES THIS PROJECT INCLUDE ELEMENTARY, JUNIOR, OR HIGH SCHOOL STUDENTS?

☒ ***No,*** go to question 11.3
☐ ***Yes,*** answer questions within table →

IF YES
Will study procedures be completed during school hours? ☐ No ☐ Yes ***If yes,*** ***Students not included in the study may view other students' involvement with the research during school time as unfair. Address this issue and how the study will reduce this outcome:*** ***Missing out on regular class time or seeing other students participate may influence a student's decision to participate. Address how the study will reduce this outcome:***
Is the school's approval letter(s) attached to this submission? ☐ Yes ☐ No, project involves Montgomery County Public Schools (MCPS) ☐ No, explain why: *You will need to obtain school approval (if involving MCPS, click here: http://www.irb.vt.edu/pages/mcps.htm). Approval is typically granted by the superintendent, principal, and classroom teacher (in that order). Approval by an individual teacher is insufficient. School approval, in the form of a letter or a memorandum should accompany the approval request to the IRB.*

11.3 DOES THIS PROJECT INCLUDE COLLEGE STUDENTS?

☒ ***No,*** go to question 12.1
☐ ***Yes,*** answer questions within table →

IF YES
Some college students might be minors. Indicate whether these minors will be included in the research or actively excluded: ☐ Included ☐ Actively excluded, describe how the study will ensure that minors will not be included:
Will extra credit be offered to subjects?

☐ No
☐ Yes

If yes,

What will be offered to subjects as an equal alternative to receiving extra credit without participating in this study?

Include a description of the extra credit (e.g., amount) to be provided within question 9.1 ("IF YES" table)

Section 12: Research Involving Minors

12.1 DOES THIS PROJECT INVOLVE MINORS (UNDER THE AGE OF 18 IN VIRGINIA)?

Note: age constituting a minor may differ in other States.

☒ ***No,*** go to question 13.1
☐ ***Yes,*** answer questions within table →

IF YES

Does the project reasonably pose a risk of reports of current threats of abuse and/or suicide?

☐ No
☐ Yes, thoroughly explain how the study will react to such reports:

Note: subjects and parents must be fully informed of the fact that researchers must report threats of suicide or suspected/reported abuse to the appropriate authorities within the Confidentiality section of the Consent, Assent, and/or Permission documents.

Are you requesting a waiver of parental permission (i.e., parent uninformed of child's involvement)?

☐ No, ***both*** parents/guardians will provide their permission, if possible.
☐ No, ***only one*** parent/guardian will provide permission.
☐ Yes, describe below how your research meets ***all*** of the following criteria (A-D):
Criteria A - The research involves no more than minimal risk to the subjects:
Criteria B - The waiver will not adversely affect the rights and welfare of the subjects:
Criteria C - The research could not practicably be carried out without the waiver:
Criteria D - (Optional) Parents will be provided with additional pertinent information after participation:

Is it possible that minor research participants will reach the legal age of consent (18 in Virginia) while enrolled in this study?

☐ No
☐ Yes, will the investigators seek and obtain the legally effective informed consent (in place of the minors' previously provided assent and parents' permission) for the now-adult subjects for any ongoing interactions with the subjects, or analysis of subjects' data? If yes, explain how:

For more information about minors reaching legal age during enrollment, visit the following link:
http://www.irb.vt.edu/pages/assent.htm

The procedure for obtaining assent from minors and permission from the minor's guardian(s) must be described in ***Section 4*** *(Consent Process) of this form.*

Section 13: Research Involving Deception

For more information about involving deception in research and for assistance with developing your debriefing form, visit our website at http://www.irb.vt.edu/pages/deception.htm

13.1 DOES THIS PROJECT INVOLVE DECEPTION?

☒ ***No,*** go to question 14.1
☐ ***Yes,*** answer questions within table →

IF YES
Describe the deception:
Why is the use of deception necessary for this project?
Describe the debriefing process:
Provide an explanation of how the study meets <u>all</u> the following criteria (A-D) for an alteration of consent: Criteria A - The research involves no more than minimal risk to the subjects: Criteria B - The alteration will not adversely affect the rights and welfare of the subjects: Criteria C - The research could not practicably be carried out without the alteration: Criteria D - (Optional) Subjects will be provided with additional pertinent information after participation (i.e., debriefing for studies involving deception): *By nature, studies involving deception cannot provide subjects with a complete description of the study during the consent process; therefore, the IRB must allow (by granting an alteration of consent) a consent process which does not include, or which alters, some or all of the elements of informed consent.*
The IRB requests that the researcher use the title "Information Sheet" instead of "Consent Form" on the document used to obtain subjects' signatures to participate in the research. This will adequately reflect the fact that the subject cannot fully consent to the research without the researcher fully disclosing the true intent of the research.

Section 14: Research Involving Existing Data

14.1 WILL THIS PROJECT INVOLVE THE COLLECTION OR STUDY/ANALYSIS OF EXISTING DATA DOCUMENTS, RECORDS, PATHOLOGICAL SPECIMENS, OR DIAGNOSTIC SPECIMENS?

Please note: it is not considered existing data if a researcher transfers to Virginia Tech from another institution and will be conducting data analysis of an on-going study.

☒ ***No,*** you are finished with the application
☐ ***Yes,*** answer questions within table →

IF YES
From where does the existing data originate?
Provide a detailed description of the existing data that will be collected or studied/analyzed:
Is the source of the data public? ☐ No, continue with the next question ☐ Yes, you are finished with this application

Will any individual associated with this project (internal or external) have access to or be provided with existing data containing information which would enable the identification of subjects:

- ***Directly*** (e.g., by name, phone number, address, email address, social security number, student ID number), or
- ***Indirectly through study codes*** even if the researcher or research team does not have access to the master list linking study codes to identifiable information such as name, student ID number, etc or
- ***Indirectly through the use of information that could reasonably be used in combination to identify an individual*** (e.g., demographics)

☐ No, collected/analyzed data will be completely de-identified
☐ Yes,

If yes,

Research will not qualify for exempt review; therefore, if feasible, written consent must be obtained from individuals whose data will be collected / analyzed, unless this requirement is waived by the IRB.

Will written/signed or verbal consent be obtained from participants prior to the analysis of collected data? -select one-

This research protocol represents a contract between all research personnel associated with the project, the University, and federal government; therefore, must be followed accordingly and kept current.

Proposed modifications must be approved by the IRB prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects.

Do not begin human subjects activities until you receive an IRB approval letter via email.

It is the Principal Investigator's responsibility to ensure all members of the research team who interact with research subjects, or collect or handle human subjects data have completed human subjects protection training prior to interacting with subjects, or handling or collecting the data.

----------END----------

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
v.10
August 28, 2019

Informed Consent for Participants
In Research Projects Involving Human Subjects

Title: Abuse liability of reduced nicotine content cigarettes: Experiment 2
Protocol: 17-244
Principal Investigators: Warren Bickel, Ph.D.
Institution: Fralin Biomedical Research Institute at VTC (formerly Virginia Tech Carilion Research Institute)

Purpose of the Study
You have been asked to come to Virginia Tech because you may qualify for this study. Your participation in this study will help us learn more about the features of cigarettes that influence economic purchasing decisions.

Organization and Funding Source
This study is being conducted by the Fralin Biomedical Research Institute at VTC (formerly Virginia Tech Carilion Research Institute) and will be funded by the National Institute on Drug Abuse/National Institutes of Health.

Number of Participants
We will enroll up to 350 participants in this study.

Participation
To participate in this study, you must be at least 18 years of age and a cigarette smoker. Women who are able to get pregnant and: are planning pregnancy, pregnant, lactating, or are not willing to use contraception for the purposes of preventing pregnancy while participating in the study are not eligible for this study.

To determine if it is appropriate for you to join this study, we will ask you to complete several questionnaires. We may stop your participation if there is evidence that you have a current unstable medical illness and/or an unmanaged psychiatric or neurological disorder. We will stop your participation if your answers or performance suggest that it is not appropriate for you to continue in the study. Violation of research center policies may result in the research team withdrawing you from the study. We may also stop your participation if you do not or are unable to complete any of the study procedures. We may also stop an ongoing session, or end your participation in the study because we have collected all the information we need.

Although you must be a current cigarette smoker to participate, participation in this study may increase your risk of harm relative to your current tobacco use.

You are free to stop your participation at any time. You may talk with other people about your decision to participate in this study, although we suggest avoiding confirming participation in this study to maintain confidentiality. You do not have to answer any questions that make you feel uncomfortable. There are no "right" or "wrong" answers; we want you to answer the questions honestly and thoughtfully. If it is appropriate for you to continue in the study, you will

then complete questionnaires and computerized tasks that will measure some of your preferences and abilities.

Description and Procedures

This study will require you to complete approximately 6 visits to this Virginia Tech facility, including today's consent session.

One (*today's*) *Consent session (approximately 1 hour)*. We will ask you some questions to make sure participation in the study is appropriate for you. We will also collect information (e.g. age, education) from you that we need to analyze our data. We will give you a detailed description of what it will be like to be in the study and answer any questions you have. We will also obtain a breath carbon monoxide (CO) reading and urine sample to test for pregnancy (females only). We will measure your intentions of quitting smoking and/or obtaining treatment.

One *Assessment session (approximately 1 hour)*. The first lab session will be an assessment session to collect information on substance use patterns and behavioral and cognitive tasks that we think may inform or compliment the results from the main study. This session may be scheduled the same day as the consent session or on a different day. These assessments will include:

- Breath and self-report measures of your recent nicotine product use
- Questionnaire about cigarette craving
- A measure of attention
- A questionnaire assessing how many nicotine products you'd purchase at different prices
- A measure of withdrawal symptoms
- A measure of your working memory
- A choice task asking you to choose between money or other commodities available at different delays
- A questionnaire on measuring your motivation to change

If you are eligible to complete the rest of the study, we will also provide you with a 5-day supply of an experimental cigarette that may have a reduced nicotine concentration. We will ask that you smoke this cigarette for the next five days instead of the cigarettes you usually smoke.

Four *Experimental Tobacco Marketplace sessions (approximately 30 minutes – 1 hour each).* In the remaining four sessions, you will be asked to make nicotine purchases in an online experimental marketplace. Some of the nicotine products will be experimental cigarettes (similar to the 5-day supply you will be given) and may or may not have reduced-nicotine content. We will give you a budget that you can use to purchase a variety of nicotine products. You will make purchases enough for the following five days. You will make these purchases when some of the nicotine products are at different prices and at the end of the session, we will randomly choose one of your purchases and we will give you with those nicotine products in exchange for money from your budget. Any money left in your budget after you make the purchases will be given to you. During the five-day periods following these Experimental Tobacco Marketplace sessions, you agree to only consume cigarettes and other nicotine products purchased in this session. You

should not share these products with other people and you should not consume products obtained from other sources.

You will come back after five days (typically scheduled a week apart) and tell us what nicotine products you used that we gave you and if you used any nicotine products that we did not provide you. You will be able to return any nicotine products that we gave you and did not use and we will give you money for those products. You will then complete the task similarly as you did initially and this will repeat until the last session. After purchasing during the last marketplace session, you will complete a questionnaire on your motivation to change, as you did during the assessment session. As the follow-up part of the last session, we will call you and ask you to report your nicotine use as you've done for the previous sessions. You may also come in and return any unused products you've purchased.

Risks/Discomforts/Inconveniences
One risk of participating in this study is possible embarrassment. This may result from answering questions that you consider sensitive. Some of our questions will ask for information about medical and psychiatric conditions and drug use. In addition, loss of confidentiality is another potential risk of participation. We will make every effort to protect your confidentiality should you participate in this study. Any expenses accrued for seeking or receiving medical or mental health treatment will be the responsibility of the subject and not that of the research project, research team, or Virginia Tech.

Due to the investigative nature of this study, there may be other risks that are currently unknown, for example feelings related to withdrawal or increased cravings.

If problems occur during the course of the study we will determine whether you should continue. If necessary, referrals will be provided. If you have questions concerning the study, please contact Mikhail Koffarnus, Ph.D., one of the Principal Investigators, at 540-526-2107 (office).

Possible Benefits
You may benefit from education about research participation. The project involves minimal risk to confidentiality or other personal rights or to physical or emotional health.

Voluntary Participation and Confidentiality
Your participation in this study is voluntary. You are free to decline participation in this study or withdraw from it at any time. If you are a Virginia Tech student, you may withdraw from the study without affecting your academic standing (i.e., your student status and evaluations will not be affected). We will act in accordance with the guidelines for the protection of human research participants issued by the Institutional Review Board (IRB) and Office of Research Compliance (ORC). Your identity on records relevant to this study will not be made public. Any publications resulting from this research will not mention your name or any other personally identifying information.

It is possible that the Institutional Review Board (IRB) may view this study's collected data for auditing purposes. The IRB is responsible for the oversight of the protection of human subjects

involved in research. The sponsor (VTCRI) or their appointed designees as well as the IRB, ORC, or other institutional oversight offices will be granted direct access to your original research records for verification of data. If your record is used or distributed for government purposes, this will be done under conditions that will protect your privacy. You will be informed of any significant new findings that may relate to your continued participation in this study.

The study team must release certain information to the appropriate authorities if at any time during the study there is concern that child abuse or elder abuse has possibly occurred or you disclose a desire to harm yourself or others.

Compensation

You will be compensated with a reloadable prepaid card issued by Greenphire ClinCard (www.myclincard.com), an FDIC-insured payment provider that specializes in clinical trial stipend payments that comply with IRB privacy regulations and considerations. At intake, you will receive a prepaid MasterCard debit card that can be used anywhere that accepts MasterCard. As payments are earned in the course of the study, additional funds will be added to your account. Funds are available within seconds when added and you can check your balance as desired. For your participation, you will be compensated:

- $20 for the consent session
- $40 for the assessment session (if you are eligible to complete the entire study, you will receive $10 for the initial part of the assessment session and $30 for returning and completing the assessment session and sampling period)
- $20 for each of the four experimental tobacco marketplace sessions
- $75 completion bonus for completing all aspects of the study

In total, you may earn up to $215. In addition to these amounts, you will also receive $6.25 to $50 per marketplace session in your study budget for use in each purchasing session. Reimbursement may also be available to offset your expenses in traveling to this Virginia Tech facility.

If you receive compensation greater than $600.00 for research participation (not limited to this study), the amount received will be reported to the IRS and you will receive an IRS 1099 Form. We will collect social security numbers and retain them for IRS and auditing purposes.

Alternative to Participation

You do not have to participate in this study if you do not wish to. The alternative to participating in this study is not participating. Your employment status, student status, grades, extra-curricular activities, or medical treatment will not be affected in any way. This is not a treatment study. If you should choose to seek treatment either before or after your participation in this study, there are a number of options. Most types of treatment for nicotine dependence involve some form of counseling and medication. A national help line, 1-800-QUITNOW (1-800-784-8669) offers free assistance and referrals.

Questions or Concerns

If you have questions about this study, please contact the Principal Investigator, Dr. Warren Bickel at 540-526-2088 (telephone) or wkbickel@vtc.vt.edu (e-mail).

If you have any questions about your rights as a research subject or concerning a research related injury, you can call the Virginia Tech Institutional Review Board for the Protection of Human Subjects at 540-231-3732 (telephone) or irb@vt.edu (e-mail).

Subject's Responsibilities

I voluntarily agree to participate in this study. I have the following responsibilities:

- I will answer questions about health, and past and current substance and alcohol use.
- I will complete laboratory assessments.
- I will not share or give away any of the nicotine products given to me by the researchers.
- During the five-day sampling and consumption periods following Experimental Tobacco Marketplace sessions, I will only consume tobacco products purchased in this study.
- I will notify the researchers if I experience any discomfort or would like to discontinue participation from this study.
- I will let the researchers know if I have any comments, questions or concerns regarding participation in this study.

Subject's Permission/Statement of Consent

The purpose and voluntary nature of this study, as well as the potential benefits and risks that are involved have been explained to me. I have read the Consent Form and conditions of the project. I have been able to ask questions and express concerns, which have been satisfactorily responded to by the study team. I have been told that I will be given a copy of this consent form. I hereby acknowledge the above and give my informed and free consent to be a participant in this study. I recognize that I am not waiving any of my rights as a research participant by signing this consent form.

Participant's printed name	Signature	Date
Principal Investigator's/Designee's printed name	Signature	Date
Person obtaining informed consent	Signature	Date

after ten 60-mL puffs with each puff initiated 30 seconds after the previous. Puff volume will be measured by a custom-built puff flowmeter available in our laboratory. Participants will be asked to consume puffs as close as possible to 60 mL each and will be given real-time on-screen feedback of their puff volume as they inhale. Consumption will occur in ventilated booths located in the Addiction Recovery Research Center specifically designed for this purpose.

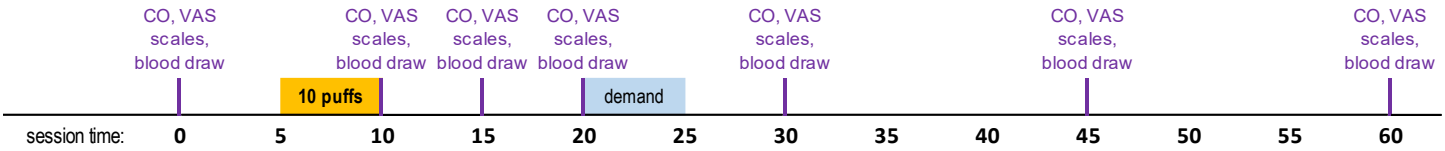

Figure 4. The sequence of events in the cigarette purchase sessions.

To measure how the subjective effects and plasma nicotine levels dissipate over the course of an hour, VAS ratings and blood draws will be collected immediately after the 5-minute administration period at minute 10, and again at minutes 15, 20, 30, 45, and 60. We will use closed intravenous catheter systems to avoid multiple needle sticks per session. At minute 20 (10 min after the end of the consumption period), participants will complete a hypothetical purchase task for the cigarette they just consumed, similar to the ones completed during the assessment session (see **Table 1**). Hypothetical purchase tasks are typically used to measure the consumption of a product already familiar to the participant. In this experiment, we will use this procedure in a novel way by asking participants to indicate their consumption decisions for a product they just consumed, but remain blinded to the nicotine content. This will prevent their responses from being biased by preconceptions of dose information, instead tying purchasing behavior to the experienced effects of each dose.

Participants will be compensated $20 for the consent session, $40 for the assessment session, $40 for each of the six cigarette purchase sessions, and $75 for completing all sessions for a maximum total of $375.

Sample Size Justification

For Aim 1 we request a sample size of n=36 completed participants. In this aim, we intend to compare demand for cigarettes across doses of nicotine. Typically, demand for a drug is not compared across doses because when price is expressed as unit dose (expenditure per mg of drug), all reinforcing doses of a drug fall on the same demand curve (Hursh & Silberberg, 2008). However, here we are explicitly intending to assess where the low-dose effect occurs for cigarettes (i.e., the dose at which consumption data no longer falls on the same unit-price curve), so we will compare demand across doses. A reanalysis of previous work (Johnson, et al., 2004) that compared demand for conventional and denicotinized cigarettes resulted in a very large effect size, which would be expected with cigarettes containing negligible amounts of nicotine. These data do not form a good basis for the present power analysis as they are an extreme case. Therefore, we have powered Experiment 1 to give us an 80% chance to detect an effect size of $f = 0.175$, which lies half way between a 'medium' and 'small' effect by convention (Cohen, 1992). This analysis was based on a within-factors ANOVA with 6 repeated measures (doses) per subject and a type 1 error rate of $\alpha = 0.05$, calculated in G*Power 3.1.9.2.

Data Analyses

Demand Analyses by Nicotine Content. In this experiment, we will compare behavioral economic demand intensity and elasticity of conventional cigarettes and reduced-nicotine cigarettes at five doses (0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, and 17.4 mg/g). Demand data will be fit to a modification (Koffarnus, et al., 2015) of a model proposed by Hursh and Silberberg (2008) to quantify the relationship between the price of a commodity and consumption of that commodity:

$$Q = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)}$$

where Q is consumption of the commodity, C is the price, Q_0 is the derived initial consumption without cost constraints (demand intensity), k is the span of the function in logarithmic units, and α is the demand elasticity. Q and C are determined by the data and k is set to a constant determined empirically by the actual data, leaving only Q_0 (demand intensity) and α (demand elasticity) as free parameters to be fitted. Analysis will proceed by fitting the above equation to individual subject data, then comparing demand intensity and elasticity consistent with the goals of each analysis. Intensity and elasticity from the demand function will be compared among the different cigarette types with nonlinear regression, as we have done previously (e.g., Koffarnus, Hall, et al., 2011; Koffarnus, et al., 2015). Then, mixed effects models will be used to characterize intensity and elasticity as a function of cigarette type. A random effect will be included to model repeated measures on subjects, and socio-economic and other demographic variables will be statistically screened for inclusion using

model-based hypothesis tests. These analyses will allow us to detect which doses fall on the same unit price curve and which doses do not and constitute a low-dose exception that we hypothesize will be related to lack of abuse liability. Additionally, we will be able to inform regulators how cigarettes at different doses are likely to affect unrestricted consumption (demand intensity) and cigarette valuation (demand elasticity).

In addition to the demand data, we will compare the VAS measures of drug effect as a function of cigarette dose to determine if these measures coincide with demand intensity, demand elasticity, or both. For these analyses, we will use mixed effects models to compare cigarette type and dose for the VAS measures and to control for the variance associated to subject in this within-subject design.

Analyses by Nicotine Absorption. We will also analyze the demand data as a function of pharmacokinetic parameters derived from the plasma nicotine data, allowing us to determine how nicotine absorption and circulating nicotine level affects demand intensity and elasticity. From the plasma nicotine curves, we can obtain measures of C_{max} (the peak plasma nicotine concentration) and the area under the plasma nicotine concentration curve, a measure of the total nicotine exposure over a given period of time. These measures will allow us to assess demand as a function of actual nicotine exposure and provide quantitative estimates of how abuse liability of cigarettes relates to nicotine exposure. Data analyses will be carried out similarly to those above, but with the pharmacokinetic variables derived from plasma nicotine levels being the basis of comparison across doses. This will allow us to calculate demand parameters in terms of plasma nicotine instead of potentially arbitrary units like puffs or cigarettes consumed. Expressing demand in terms of plasma nicotine is important as it will allow us to project what the relative abuse liability and consumption of cigarettes would be across a range of obtained nicotine concentrations, independent of particulars of nicotine delivery among users or cigarettes (*i.e.,* control for nicotine absorption by the lungs, puff velocity, etc.). This information would be very valuable to regulators, as it would allow them to create policy based on nicotine dose.

Expected Results

Understanding how demand for nicotine products relates to nicotine content and nicotine absorption is important for the effective regulation of nicotine content. We expect that demand will be related to plasma nicotine levels and nicotine content of the cigarettes, but that this will not be a strict one to one relationship. We expect this relationship to be more straightforward between the 5.6 and 17.4 mg/g doses, but that that this will become less clear and break down at small doses approaching 0 mg/g (i.e., a low-dose exception). In Specific Aim 1, we will quantify this relationship between dose and demand, which will also result in the quantification of the demand associated with cigarettes delivering negligible nicotine.

Experiment 2: Model Potential Regulatory Environments with our Experimental Tobacco Marketplace

In this experiment, we will ascertain the impact of reduced-nicotine on consumption of multiple products in the complex tobacco marketplace. We will assess control conditions and two regulatory environments directly relevant to the introduction of reduced-nicotine cigarettes to the current tobacco marketplace.

Participants

174 current cigarette smokers will be recruited from the community surrounding Roanoke, VA with the same eligibility criteria as in Experiment 1. We expect that approximately 14% of these participants will drop-out prior to completion based on a recent experiment with a similar population and time commitment, leaving 150 participants (30 in each of five dose groups) with complete data (chosen based on a power analysis below).

Procedure

Each participant will be randomly assigned to a dose group matching one of the reduced-nicotine cigarettes from Experiment 1 (0.4 mg/g, 1.4 mg/g, 2.5 mg/g, 5.6 mg/g, and 17.4 mg/g). Random assignment will be double blind, such that the participant and any research staff directly interacting with the participant will not be aware of the assigned cigarette dose. After granting informed consent, participants will complete an assessment session, a sampling period to familiarize them with their assigned cigarette dose, and four Experimental Tobacco Marketplace sessions. Participants will not be asked to be abstinent from nicotine prior to experimental sessions. The participants who enroll into the experiments and either complete or drop out will be illustrated according to the revised Consolidated Standards of Reporting Trials (CONSORT) statement (Moher, et al., 2001).

Assessment Session. The first session will be an assessment session to collect information from participants on substance use patterns and severity, as well as the results of behavioral and cognitive tasks that we think may inform or complement the results from the main study. The same set of assessments as in Experiment 1 will be used (**Table 1**).

cigarettes, usual brand of cigarettes, and other nicotine products will all be available, mimicking a regulatory environment where reduced-nicotine cigarettes are made available in the marketplace, but conventional cigarettes remain available as well. This condition will include double the pricing scenarios such that both reduced-nicotine and conventional cigarettes will alternately serve as the modified-price and constant-price commodity, allowing us to measure symmetrical cross price elasticity for conventional and reduced-nicotine cigarettes (**Table 2**). Participants will be compensated $20 for the consent session, $40 for the assessment session, $20 for each of the four Experimental Tobacco Marketplace sessions, $20 in experimental income to be kept and/or used for tobacco/nicotine products in the Experimental Tobacco Marketplace sessions, and $75 for completing all sessions for a maximum total of $295.

Sample Size Justification

For Aim 2, we request a total sample size of n=150 completed participants (30 per dose). The goal of Aim 2 is to analyze condition effects within each dose. To estimate an effect size for this experiment, the same paper (Johnson, et al., 2004) used in Aim 1 was used to estimate the effect of introducing reduced-nicotine cigarettes into a condition containing conventional cigarettes and an alternate commodity (nicotine gum in the previous paper), one of the main analysis types we intend to do (see below). In this paper, using a reanalysis similar to that described above, making denicotinized cigarettes available in addition to conventional cigarettes and gum reduced the substitution of nicotine gum, which was associated with an effect size of $f = 0.382$, which is near to a 'large' effect by convention (Cohen, 1992). Due to the multifaceted nature of the analyses in Aim 2, we chose a more conservative effect size of $f = 0.25$, a 'medium' effect. Using this effect size, our power analysis yielding 30 participants per dose based on a within-factors ANOVA for each individual dose, 4 repeated measures (conditions), a type 1 error rate of $\alpha = 0.05$, and 90% statistical power. Further, our tests include the statistical interaction between dose and scenario using a within-between interaction ANOVA model. With the requested sample size, we will have sufficient statistical power to detect interaction effects of $f = 0.14$, close to a 'small' effect size. Hence, we have ample statistical power to detect meaningful effects in this study. These analyses were performed in G*power version 3.1.9.2.

Data Analyses

General Demand Analysis Procedure. The nonlinear regression demand analyses to obtain subject-specific measures of intensity and elasticity are analogous to Aim 1. To satisfy the goals of Aim 2, data will be further analyzed as described below.

General Substitution Analyses Procedure. Aim 2 involves a number of comparisons of substitution among products in the four scenarios in addition to the demand-style analyses in Aim 1. To address the substitution goals we will use a modification analogous to that we've used before (Koffarnus, et al., 2015) of an equation proposed by Hursh and Roma (2013), which relates consumption of a fixed-price commodity (*e.g.*, a non-combustible nicotine product in condition **a** of **Table 2**) as price of a primary commodity (*e.g.*, usual brand of cigarettes in condition **a**) changes:

$$Q = Q_{alone} * 10^{I*e^{-\beta C}}$$

In this equation, Q_{alone} represents the maximum consumption of the fixed-price commodity when the primary commodity has a price high enough to drive consumption to zero, β is the sensitivity of fixed-price commodity consumption to the price of the primary commodity, I is an interaction parameter that indicates whether the fixed-price commodity is a substitute (positive I value), complement (negative I value), or independent (I value near zero), and Q and C represent consumption of the fixed-price commodity and cost of the primary commodity, respectively, and are known from data. This equation has three parameters (Q_{alone}, I, and β) that will be estimated from experimental data using nonlinear regression. Analysis will proceed similarly as in Aim 1 with the substitution equation being fit to individual subject data to generate subject-specific estimates of maximum consumption, interaction, and sensitivity. These values will then be further analyzed to satisfy the goals of Aim 2.

Primary Analyses of Interest in Aim 2. Aim 2 involves a number of comparisons between demand characteristics (intensity and elasticity) and substitution (maximum consumption, sensitivity, interaction) across and within both doses and conditions involving three types of commodities (reduced-nicotine cigarettes, conventional cigarettes, and other non-combustible products). Within-dose statistical comparisons are briefly described in **Table 2**. Each of these effects will also be compared in larger mixed-effect models across dose with dose entered as a between-subject variable to determine the degree to which these substitution and demand effects differ by dose.

1. Compare substitution (maximum consumption, sensitivity, and interaction) of conventional cigarettes for reduced-nicotine cigarettes and vice versa in condition **d**. In separate pricing scenarios, this condition will include both conventional and reduced-nicotine cigarettes as a constant-price and modified-price commodity, allowing us to assess the degree to which the two cigarette types substitutes for one another. This analysis will inform regulators the degree to which reduced-nicotine cigarettes will, at each of the doses included here, replace conventional cigarettes in the marketplace as a functionally equivalent commodity (substitutes) or act independently in the marketplace without affecting consumption of the other cigarette (independents).
2. This analysis will compare demand intensity and elasticity of reduced-nicotine cigarettes across conditions **b**, **c**, and **d**, informing regulators of the degree to which consumption of reduced-nicotine cigarettes at each of the doses studied here changes as a function of the other nicotine products present in the marketplace, including conventional cigarettes.
3. This analysis is analogous to analysis **2**, but will compare demand intensity and elasticity of conventional cigarettes across conditions **a** and **d**, informing regulators of the degree to which consumption of conventional cigarettes is affected by the presence or absence of reduced-nicotine cigarettes in the marketplace at each reduced-nicotine dose.
4. This analysis will also compare whether cross-price elasticity parameters (maximum consumption, sensitivity, and interaction) for non-combustible products change when reduced-nicotine cigarettes are added to the current marketplace in addition to conventional cigarettes (**a** versus **d**), and when reduced-nicotine cigarettes replace conventional cigarettes in the marketplace (**a** versus **c**). These analyses will inform regulators how the introduction of reduced-nicotine cigarettes at each dose included here will affect the overall nicotine product marketplace and influence consumption of other nicotine products.
5. This analysis will compare substitution of other nicotine products for reduced-nicotine cigarettes with (condition **d**) and without (condition **c**) conventional cigarettes in the marketplace. This analysis will inform regulators how, under circumstances where reduced-nicotine cigarettes are present in the marketplace at one of the doses studied here, removal of conventional cigarettes will affect consumption of other nicotine products also present in the marketplace.

To complete the analyses in Aim 2, a random effect will be included to model any subject effect, and socio-economic and other demographic variables will be statistically screened for inclusion using model-based hypothesis tests.

Difficulties and Limitations

Participant retention may be a limitation. This study requires repeated laboratory visits with a period of nicotine abstinence preceding most visits in Experiment 1, which may difficult for some participants to accomplish. We have experience successfully completing studies with similar lab visit requirements, and to counteract this difficulty, we have budgeted for a projected dropout rate appropriate for each experiment based on previous experiments conducted in our lab with similar visit and abstinence requirements.

Those that drop out in Experiment 1 may be more likely to be heavy smokers who find the abstinence criterion more difficult, which could bias our results. To mitigate this limitation, we will perform an analysis of participants who drop out versus those who remain enrolled to detect any demographic differences or nicotine product use pattern differences and incorporate any differences as covariates in our statistical analysis where appropriate.

Project Timetable

Over the course of the three-year grant period, Experiment 1 will be completed in year 1 and Experiment 2 will be completed in years 2 and 3. The first 2 months of Experiment 1 will be allocated toward preparing for this experiment (i.e., training staff, preparing standard operating procedures, purchasing supplies, etc.), allowing 10 months to recruit and run the estimated 58 participants needed to complete 36 participants, or an average of 5.8 participants per month. Data analysis and manuscript preparation for this experiment will be completed in year 2 concurrently with the running of Experiment 2. The first 2 months of Experiment 2 in year 2 will be allocated to preparing for this experiment, with the final 2 months of year 3 allocated toward data analysis and manuscript preparation, leaving 20 months to recruit and run the estimated 174 participants needed to complete 150 participants, or an average of 8.7 participants per month. Over the past 12 months, studies in our laboratory with cigarette smokers as participants maintained an average of 30.8 participants enrolled per month. This far exceeds our requirements for the proposed enrollment goals for the proposed Experiment 1 (5.8 per month) and Experiment 2 (8.7 per month), assuring that we will be able to obtain the requisite number of eligible participants.